Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients With Acute Coronary Syndromes

PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries - Implementation of FFR [Fractional Flow Reserve] in Routine Practice)

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Background—Fractional flow reserve (FFR) is not firmly established as a guide to treatment in patients with acute coronary syndromes (ACS). Primary goals were to evaluate the impact of integrating FFR on management decisions and on clinical outcome of patients with ACS undergoing coronary angiography, as compared with patients with stable coronary artery disease.

Methods and Results—R3F (French FFR Registry) and POST-IT (Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease), sharing a common design, were pooled as PRIME-FFR (Insights From the POST-IT and R3F Integrated Multicenter Registries - Implementation of FFR in Routine Practice). Investigators prospectively defined management strategy based on angiography before performing FFR. Final decision after FFR and 1-year clinical outcome were recorded. From 1983 patients, in whom FFR was prospectively used to guide treatment, 533 sustained ACS (excluding acute ST-segment–elevation myocardial infarction). In ACS, FFR was performed in 1.4 lesions per patient, mostly in left anterior descending (58%), with a mean percent stenosis of 58±12% and a mean FFR of 0.82±0.09. In patients with ACS, reclassification by FFR was high and similar to those with non-ACS (38% versus 39%; *P*=NS). The pattern of reclassification was different, however, with less patients with ACS reclassified from revascularization to

Received October 5, 2016; accepted May 22, 2017.

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The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.116.004296/-/DC1.

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medical treatment compared with those with non-ACS (*P*=0.01). In ACS, 1-year outcome of patients reclassified based on FFR (FFR against angiography) was as good as that of nonreclassified patients (FFR concordant with angiography), with no difference in major cardiovascular event (8.0% versus 11.6%; *P*=0.20) or symptoms (92.3% versus 94.8% angina free; *P*=0.25). Moreover, FFR-based deferral to medical treatment was as safe in patients with ACS as in patients with non-ACS (major cardiovascular event, 8.0% versus 8.5%; *P*=0.83; revascularization, 3.8% versus 5.9%; *P*=0.24; and freedom from angina, 93.6% versus 90.2%; *P*=0.35). These findings were confirmed in ACS explored at the culprit lesion. In patients (6%) in whom the information derived from FFR was disregarded, a dire outcome was observed.

Conclusions—Routine integration of FFR into the decision-making process of ACS patients with obstructive coronary artery disease is associated with a high reclassification rate of treatment (38%). A management strategy guided by FFR, divergent from that suggested by angiography, including revascularization deferral, is safe in ACS. **(*Circ Cardiovasc Interv*. 2017;10:e004296. DOI: 10.1161/CIRCINTERVENTIONS.116.004296.)**

Key Words: acute coronary syndrome ■ coronary artery disease ■ coronary angiography ■ fractional flow reserve ■ mortality

Fractional flow reserve (FFR)–guided revascularization has been shown to be superior to angio-guided percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in reducing both short- and long-term major cardiovascular events (MACEs; including death and myocardial infarction)[1,2] and deferral of nonischemic lesions is associated with excellent outcomes.[3] Several studies that have included mostly stable patients have suggested that routine use of FFR is associated with a high rate of reclassification and change in management decisions (up to 44%) and that treatment reallocation (against angiography) is safe.[4–8]

Patients sustaining an acute coronary syndrome (ACS) currently make up the majority of patients considered for coronary revascularization.[9] Invasive management of patients with ACS, including coronary angiography and revascularization (when needed), is the one situation where a potential mortality benefit has been demonstrated.[10] Still, there is a clear need to further optimize clinical decision making in this important patient subset.

Concerns about microcirculatory responsiveness during the acute setting have undermined the use of FFR in patients with ACS.[11] Although dedicated physiological studies have demonstrated that measurement of FFR can be relevant in the context of ACS,[12–14] clinical evidence supporting it's use, particularly in the setting of non–ST-segment–elevation myocardial infarction (NSTEMI), is based on the results of relatively small clinical outcome studies and subgroup analysis.[7,15] In addition, there is currently no report of the impact of routine use of FFR in the decision-making process in patients with ACS. Large studies, powered for clinical outcomes, are therefore needed to assess the integration of routine FFR measurement into the management of patients with ongoing or recent ACS.

In addition to dedicated randomized trials,[2,16] large nationwide studies, such as R3F and POST-IT,[6,17] have contributed to deciphering how FFR can be integrated into patient management and impact clinical outcomes and have been of major importance for the implementation of FFR in clinical practice. In the large multicenter PRIME-FFR joint international prospective study (POST-IT and R3F Integrated Multicenter Registries - Implementation of FFR in Routine Practice),[6,17] we aimed to assess the extent of treatment change by routine use of FFR in patients with ACS and the safety of reclassification and revascularization deferral as compared with stable patients.

WHAT IS KNOWN

- In patients with stable coronary artery disease, fractional flow reserve (FFR) has been shown to change the revascularization decision in up to 44% of patients, whereas FFR-guided revascularization decision has been shown to improve clinical outcomes and reduce costs.
- The value of FFR-guided revascularization decision in patient with acute coronary syndrome (ACS) remains unclear.

WHAT THE STUDY ADDS

- In patients with ACS, FFR is associated with a high rate of change of the revascularization strategy (38%), as high as in patients with non-ACS.
- In patients with ACS, integrating FFR information to reclassify patient management is safe, and, in particular, FFR-based deferral to medical treatment is as safe as it is in patients with non-ACS.
- In patients with ACS, disregarding the information derived from FFR is associated with a dire outcome.

Methods

Patient Population

The total population (n=1983) results from the merge of the R3F and the POST-IT cohorts.[6,17] These nationwide prospective studies share a common design and objective, dedicated to investigate the routine use of FFR at the time of diagnostic angiography and its impact on patient management decisions and on 1-year clinical outcome. Specifically, the R3F study included 1075 consecutive patients with at least 1 angiographically ambiguous lesion (35%–65% by visual estimate) in a major epicardial coronary vessel evaluated by FFR in 20 French centers (October 2008 to June 2010). Similarly, the POST-IT study included 918 patients at 19 Portuguese centers (March 2012 to November 2013) and was designed to prospectively include all consecutive patients referred for angiography in whom at least 1 intermediate lesion at a major epicardial coronary vessel was evaluated by FFR.

In both studies, baseline, clinical, and angiographic parameters were prospectively recorded in an electronic case report form. Relevant institutional review boards and ethics committees approved the research

protocols. All patients provided written informed consent for clinical follow-up and for both storage and use of their clinical data.

Management Strategy, Reclassification, and Deferral Definitions

As part of the e-CRF, investigators were asked to define prospectively their a priori management strategy for each patient, based on angiography and available clinical information before FFR measurement and then, after FFR was performed, to define their final strategy. The use (or not: disregarded) of the FFR information to achieve the final management decision was also prospectively recorded.

This decision could be medical therapy (with or without additional stress test), PCI, or CABG. Patients in whom a hybrid approach was chosen were classified as CABG. When a final decision of revascularization was reached for the patient, it could be performed immediately (PCI) or at later stage (PCI or CABG). Reclassification of patient management strategy was defined as a difference (or discordance) between the a priori and the final strategies. Revascularization deferral was identified when the final strategy was medical treatment for all lesions after performing the FFR measurement (no revascularization performed or planned).

Detailed Objectives

The primary objective was to describe and evaluate the safety of routine FFR use in patients with ACS undergoing diagnostic coronary angiography disclosing at least 1 visually intermediate lesion. In particular, we aimed to

1. describe the rate of reclassification of the patient management strategy and to evaluate the safety of such reclassification. For that purpose, we compared the occurrence of 1-year MACE according to the agreement or divergence of the FFR-guided final decision with the a priori strategy suggested by angiography and
2. describe the rate of revascularization "deferral" and to evaluate its safety by comparing the occurrence of 1-year MACE in ACS-deferred patients versus "ACS-revascularized" and "non-ACS-deferred" patients.

Secondary analyses aimed at evaluating (1) the impact of reclassification and deferral on angina status at 1-year follow-up; (2) the outcome of patients in whom the results of FFR measurement were disregarded by the investigators for deciding the final management strategy; and (3) the consistency of the primary objective in (a) patients with ongoing NSTEMI/UA (unstable angina) (which represent the most acute patients in our study population) and (b) in those investigated at the culprit vessel; this was done by focusing on patients with single-vessel disease ACS because this is the only clinical situation in which the culprit nature of the investigated vessel can be ascertained.[13]

Definition of ACS and Recording of Baseline Characteristics

The presence of an ACS and classification as NSTEMI/UA or STEMI was defined at the time of inclusion according to current recommendations.[18,19] More specifically, UA/NSTEMI was defined as the combination of at least 2 of the 3 following criteria: (1) chest pain, (2) troponin rise, or (3) ischemic ECG changes.[18] Patients with NSTEMI/UA were classified as ongoing if the procedure was performed within 48 hours after symptom onset (typically within 24 hours of admission). After that, time window NSTEM/UA was classified as recent. Patients with STEMI undergoing primary PCI were not considered for enrollment in either R3F or POST-IT[6,17] and thus were not represented in the final cohort. However, they could be included after the acute phase as recent ACS, typically if a nonculprit lesion was being evaluated in a second procedure (see Methods in the Data Supplement for further details).

Angiography and FFR Procedure

Angiography was performed according to the standard practice. Qualitative description of the angiography, including the number of diseased vessels, American College of Cardiology/American Heart Association (ACC/AHA) lesion classification, and quantitative (reference diameter, percent stenosis, and length) description of the FFR-investigated lesions was recorded.

FFR measurement was performed after recording of angiographic parameters, according to the local standard practice. FFR could be done using diagnostic or interventional catheters after injection of intracoronary nitrate. Extensive FFR evaluation was not mandated per protocol, and investigators were left free to decide which vessels and lesions to interrogate. Hyperemia was achieved using high adenosine dose administered through either intracoronary bolus (≥100 µg) or intravenous infusion (140 µg/kg per minute).

Clinical Follow-Up and End Points

One-year clinical follow-up was recorded in all patients, and independent monitoring was performed in both studies. Angina status was obtained at 12-month follow-up. The study primary end point (MACE) was a composite of all-cause death, myocardial infarction, or unplanned revascularization. Each individual end point was reviewed and adjudicated by an independent clinical event committee. Myocardial infarction was defined according to the third 2012 ESC/ACCF/AHA/WHF (European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation) universal definition of MI.[20] Revascularization was considered unplanned when it was not performed or planned at the time of the index procedure. Thus, both elective staged PCI and elective CABG resulting from the index FFR evaluation were not considered as events.

Statistical Analysis

Before merging R3F and POST-IT into the PRIME-FFR data set, comparisons were made to verify that there were no major differences between the main baseline characteristics of study patients (including epidemiological, clinical, and angiographic characteristics and FFR) and in the 1-year clinical outcome of the 2 study cohorts, both overall and inside each subgroup (ACS and non-ACS). Also, to check for the consistency of the results, we replicated the POST-IT analysis on the 3RF population and vice versa.

Continuous variables are presented as mean±SD. Discrete variables are presented as absolute numbers and percentages. For patient-related characteristics, differences among groups were evaluated using Student t test or χ^2 test, as appropriate. The initial and final management strategy (medical therapy, PCI, and CABG) and overall decision to reclassify were evaluated using Fisher exact test. FFR was compared between ACS and non-ACS according to lesion stenosis severity. For that purpose, stenosis severity was stratified into 4 groups based on prespecified ranges and FFR values in each stratification group were compared using the Wilcoxon rank-sum test.

Cumulative rates of MACE were estimated using the Kaplan–Meier method, and differences between strategies were tested using Cox proportional hazards model. Multivariable Cox proportional hazards models were performed adjusting for baseline clinical and angiographic characteristics. Multiple imputation was used to account for missing covariate data in the Cox proportional hazards models. A standard imputation model with discriminant function created 10 imputed data sets for each model. The Cox model was applied to each imputed data set. Final summary results were produced by pooling the individual proportional hazards estimates, accounting for the SE within and between the models. Additional details are provided in the Methods in the Data Supplement. Analyses were conducted using the SAS system (SAS v9.4; SAS Institute, Cary, NC).

Results

Clinical Characteristics

Study population included 1983 patients, of whom 533 (27%) underwent coronary angiography and routine FFR evaluation in the context of an ACS (Table 1; Figure 1). Among patients with ACS, 43% had an ongoing NSTEMI/UA, 40% a recent NSTEMI/UA, and 17% a recent STEMI. These patients with

Table 1. Baseline Clinical Characteristics According to FFR Use and Patient Reclassification of the Management Strategy

	ACS Population						Non-ACS Population						
	Total ACS Population (n=533)	FFR Disregarded (n=34)	FFR Used (n=499)			*P* Value†	Total Non-ACS (n=1450)	FFR Disregarded (n=97)	FFR Used (n=1353)			*P* Value‡	*P* Value*
			Reclassified (n=188)	Nonreclassified (n=311)	*P* Value§				Reclassified (n=531)	Nonreclassified (n=822)	*P* Value‖		
Demographics													
Age, y	64.0±11.5	65.2±8.9	63.0±11.6	64.5±11.6	0.158	0.434	65.3±10.1	65.0±9.9	64.4±10.1	65.9±10.0	0.009	0.769	0.019
Male sex, n (%)	401 (75.2)	28(82.4)	146 (77.7)	227 (73.0)	0.245	0.320	1102 (76.0)	72 (74.2)	415 (78.2)	615 (74.8)	0.160	0.672	0.724
Cardiovascular risk factors, n (%)													
Diabetes mellitus	160 (30.8)	12 (36.4)	56 (30.8)	92 (30.3)	0.907	0.477	541 (38.2)	36 (37.5)	213 (41.0)	292 (36.5)	0.100	0.887	0.003
Hypertension	365 (70.3)	20 (60.6)	128 (70.3)	217 (71.4)	0.805	0.206	1073 (75.7)	71 (74.0)	385 (74.0)	617 (77.0)	0.215	0.676	0.016
Smoking	234 (43.9)	15 (44.1)	89 (47.3)	130 (41.8)	0.215	0.902	558 (38.5)	30 (30.9)	227 (42.7)	301 (36.6)	0.047	0.040	0.091
High cholesterol	335 (64.9)	21 (63.6)	117 (64.6)	197 (65.2)	0.895	0.873	1044 (73.8)	74 (77.1)	389 (75.1)	581 (72.6)	0.320	0.453	<0.001
Prior clinical history, n (%)													
Myocardial infarct.	187 (44.3)	13 (43.3)	72 (46.8)	102 (42.9)	0.448	0.911	360 (31.0)	28 (34.1)	134 (32.4)	198 (29.7)	0.353	0.517	<0.001
PCI	199 (47.2)	17 (56.7)	77 (50.0)	105 (44.1)	0.254	0.279	538 (46.1)	43 (51.2)	197 (47.5)	298 (44.7)	0.370	0.335	0.720
CABG	11 (2.6)	1 (3.3)	5 (3.2)	5 (2.1)	0.482	0.795	56 (4.8)	4 (4.8)	22 (5.3)	30 (4.5)	0.548	0.986	0.054
LVEF≤50%	84 (15.8)	5 (14.7)	35 (18.6)	44 (14.1)	0.410	0.444	249 (17.2)	18 (18.6)	99 (18.6)	132 (16.1)	0.362	0.928	0.757
Type of ACS							NA	NA	NA	NA	NA	NA	NA
Ongoing NSTEMI/UA	229 (43.0)	15 (44.1)	75 (39.9)	139 (44.7)	0.218	0.166	NA	NA	NA	NA	NA	NA	NA
Recent NSTEMI/UA	213 (40.0)	17 (50.0)	83 (44.1)	113 (36.3)			NA	NA	NA	NA	NA	NA	NA
Recent STEMI	91 (17.1)	2 (5.9)	30 (16.0)	59 (19.0)			NA	NA	NA	NA	NA	NA	NA
No. of diseased vessels (>50%), n (%)													
0	73 (13.7)	2 (5.9)	14 (7.4)	57 (18.3)	<0.001	0.514	268 (18.5)	9 (9.3)	53 (10.0)	206 (25.1)	<0.001	0.035	0.055
1	211 (39.6)	13 (38.2)	66 (35.1)	132 (42.4)			578 (39.9)	36 (37.1)	236 (44.4)	306 (37.2)			
2	156 (29.3)	12 (35.3)	61 (32.4)	83 (26.7)			384 (26.5)	34 (35.1)	160 (30.1)	190 (23.1)			
3	93(17.4)	7 (20.6)	47 (25.0)	39 (12.5)			220 (15.2)	18 (18.6)	82 (15.4)	120 (14.6)			
No. of lesions evaluated per patient, n (%)													
1	391 (73.4)	16 (47.1)	132 (70.2)	243 (78.1)	0.157	0.005	1049 (72.3)	46 (47.4)	380 (71.6)	623 (75.8)	0.007	<0.001	0.921
2	103 (19.3)	13 (38.2)	42 (22.3)	48 (15.4)			300 (20.7)	31 (32.0)	110 (20.7)	159 (19.3)			
≥3	39 (7.3)	5 (14.7)	14 (7.4)	20 (6.5)			101 (7.0)	20 (20.6)	41 (7.8)	40 (4.9)			

(*Continued*)

Table 1. Continued

	ACS Population						Non-ACS Population						
	Total ACS Population (n=533)	FFR Disregarded (n=34)	FFR Used (n=499)				Total Non-ACS (n=1450)	FFR Disregarded (n=97)	FFR Used (n=1353)				
			Reclassified (n=188)	Nonreclassified (n=311)	*P* Value§	*P* Value†			Reclassified (n=531)	Nonreclassified (n=822)	*P* Value‖	*P* Value‡	*P* Value*
Cardiovascular medication, n (%)													
Dual antiplatelet	314 (60.2)	22 (64.7)	117 (63.9)	175 (57.4)	0.153	0.575	742 (51.6)	48 (50.0)	303 (57.5)	391 (48.0)	<0.001	0.740	<0.001
Statin	398 (76.2)	28 (82.4)	142 (78.5)	228 (74.3)	0.297	0.387	1119 (78.0)	79 (82.3)	424 (80.6)	616 (75.9)	0.042	0.297	0.402
ACEI/ARB	319 (62.3)	20 (58.8)	117 (65.7)	182 (60.7)	0.269	0.665	839 (58.9)	56 (59.6)	319 (61.0)	464 (57.4)	0.196	0.887	0.175
β-blockers	318 (61.6)	26 (76.5)	122 (67.4)	170 (56.5)	0.017	0.066	880 (61.6)	63 (66.3)	331 (63.3)	486 (60.0)	0.229	0.330	0.999
Initial decision, n (%)													
CABG	32 (6.0)	2 (5.9)	12 (6.4)	18 (5.8)	0.944	1.000	85 (5.9)	5 (5.2)	39 (7.3)	41 (5.0)	<0.001	0.219	0.754
PCI	188 (35.3)	12 (35.3)	65 (34.6)	111 (35.7)			538 (37.1)	44 (45.4)	231 (43.5)	263 (32.0)			
Medical therapy	313 (58.7)	20 (58.8)	111 (59.0)	182 (58.5)			827 (57.0)	48 (49.5)	261 (49.2)	518 (63.0)			
Final decision, n (%)													
CABG	50 (9.4)	2 (5.9)	30 (16.0)	18 (5.8)	<0.001	0.693	140 (9.7)	9 (9.3)	90 (16.9)	41 (5.0)	<0.001	0.763	0.040
PCI	223 (41.8)	16 (47.1)	96 (51.1)	111 (35.7)			518 (35.7)	38 (39.2)	217 (40.9)	263 (32.0)			
Medical therapy	260 (48.8)	16 (47.1)	62 (33.0)	182 (58.5)			792 (54.6)	50 (51.5)	224 (42.2)	518 (63.0)			

ACS indicates acute coronary syndrome; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor antagonist; CABG, coronary artery bypass grafting; FFR, fractional flow reserve; LVEF, left ventricle ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

**P* values comparing ACS vs non-ACS populations.

†*P* values comparing in ACS FFR used vs FFR disregarded populations.

‡*P* values comparing in non-ACS FFR used vs FFR disregarded populations.

§*P* values comparing in FFR used, ACS reclassified vs ACS nonreclassified populations.

‖*P* values comparing in FFR used, non-ACS reclassified vs non-ACS nonreclassified populations.

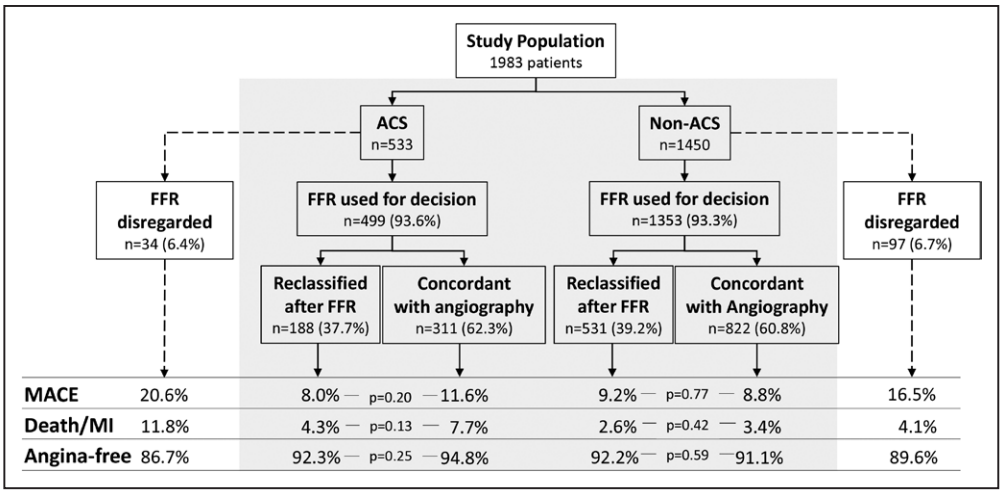

Figure 1. Study flow chart and safety of the fractional flow reserve (FFR)–based-reclassification the revascularization strategy according to acute coronary syndrome (ACS) status. The 1-y outcome of patients with ACS reclassified to a different strategy based on FFR (FFR discordant from angiography) was as good as in nonreclassified patients (FFR concordant with angiography) both in terms of major cardiovascular event (MACE) and in the of proportion of patients angina free. MI indicates myocardial infarction.

ACS had a typical clinical profile of such a population; when compared with patients with non-ACS, they were younger, more likely smokers, but less likely to have conventional risk factors (Table 1). They also had a more frequent history of previous ACS and were more likely to be treated with dual antiplatelet therapy at the time of angiography.

FFR and Angiographic Characteristics

In patients with ACS, single-vessel (0–1) and multivessel (2–3) angiographically defined coronary artery disease (CAD) were observed in 53% and 47%, respectively. FFR was performed in 1.4 lesions per patient (≥2 lesions in 27%). Overall, intracoronary adenosine was used in 54.3% of the evaluations (and conversely, the systemic intravenous route was used in the remainder). The investigated lesion was located on the left anterior descending artery in 58% of cases and was proximally located in 33% of cases. Mean percent diameter stenosis was 57% by visual estimate, and it was a typical intermediate lesion (<70% stenosis) in three fourth of cases (Table 2).

Lesions investigated in patients with ACS were slightly (but not significantly) more severe on angiographic appearance (proportion of lesions ≥70% by visual estimate: 22.8% versus 19.9%; *P*=0.10; Table 2) and definitely more complex than in patients with non-ACS (B2/C: 42% versus 38%; *P*=0.02; Table 2). Mean FFR (0.82±0.09 versus 0.82±0.10; *P*=0.76; Table 2; Figure 2A and 2C) and the relationship between angiographic percent stenosis severity and FFR were similar between patients with ACS and non-ACS (Figure 2C; Figure I in the Data Supplement). Importantly, within each category of stenosis severity, FFR was lower in more complex lesions (B2/C versus A/B1; Table I in the Data Supplement). Consistent with this observation, multivariable analyses of clinical and angiographic parameters associated with the FFR value identified the same predictors in patients with both ACS and non-ACS: age, left anterior descending location, ACC/AHA lesion type, percent stenosis, lesion length, and number of diseased vessels (Table II in the Data Supplement).

ACS Status and Clinical Outcome

In the overall ACS population, regardless of FFR result and FFR-based decision, the rates of MACE and of death/MI at 1 year were 10.9% and 6.8%, respectively, which were higher than in the non-ACS group (9.5% and 3.2%, with *P*=0.34 and *P*<0.01, respectively). The proportion of patients free from angina at 1 year was similar in patients with ACS and non-ACS (93% versus 91%; *P*=0.45).

FFR-Based Reclassification of the Management Strategy

In the vast majority of procedures (94%; n=1869), physicians used the information provided by FFR to drive their final management decision. The proportion of cases where FFR was used for decision was similar in patients with ACS and non-ACS (Figure 1; Table 1). In these patients, the overall rate of FFR-based reclassification of treatment strategy was similar in ACS and non-ACS (38% versus 39%; *P*=0.55; Table 1; Figure 3A). However, as illustrated in Table 1, Figure 3B and 3C, and Figure II in the Data Supplement, the reclassification pattern diverged significantly between patients with ACS and non-ACS. Reclassification resulted in an increase in the proportion of patients who were revascularized in both subgroups, but significantly more so in the ACS population (+26% versus +7%; *P*=0.03). Consequently, relative to baseline decision, the proportion of patients submitted to PCI or CABG after FFR was known (final decision) was higher in the ACS group than in the non-ACS group (51.1% versus 45.2%; *P*=0.02; Table 1; Figure II in the Data Supplement).

Baseline clinical and angiographic characteristics of the 719 patients (n=188 ACS and n=531 non-ACS) in whom the use of FFR was associated with reclassification of the management strategy are presented in Tables 1 and 2. Although purely clinical characteristics were similar between reclassified and nonreclassified patients (Table 1), those reclassified were more likely to have 2- to 3-vessel CAD (*P*<0.001), an left anterior descending lesion (*P*<0.006), and a lower FFR value (*P*<0.001).

Table 2. Baseline Angiographic Characteristics According to Patient and Lesion Reclassification of the Management Strategy and FFR Used

	ACS Population						Non-ACS Population						
	Total ACS Lesions (n=720)	FFR Disregarded (n=36)	FFR Used (n=684)				Total Non-ACS Lesions (n=1978)	FFR Disregarded (n=109)	FFR Used (n=1869)				
			Reclassified (n=247)	Nonreclassified (n=437)	*P* Value§	*P* Value†			Reclassified (n=703)	Nonreclassified (n=1166)	*P* Value‖	*P* Value‡	*P* Value*
Lesion location, n (%)													
Left anterior descending	414 (57.7)	25 (69.4)	163 (66.0)	226 (52.0)	0.006	0.460	1146 (57.9)	77 (70.6)	437 (62.2)	632 (54.2)	0.003	0.074	0.025
Circumflex	138 (19.2)	3 (8.3)	43 (17.4)	92 (21.1)			294 (14.9)	10 (9.2)	102 (14.5)	182 (15.6)			
Right coronary artery	132 (18.4)	7 (19.4)	33 (13.4)	92 (21.1)			407 (20.6)	16 (14.7)	132 (18.8)	259 (22.2)			
Left main	32 (4.5)	1 (2.8)	7 (2.8)	24 (5.5)			117 (5.9)	6 (5.5)	30 (4.3)	81 (6.9)			
Bypass	2 (0.3)	0 (0.0)	1 (0.4)	1 (0.2)			14 (0.7)	0 (0.0)	2 (0.3)	12 (1.0)			
Any proximal lesion, n (%)	239 (33.3)	15 (41.7)	76 (30.8)	148 (34.0)	0.385	0.274	687 (34.7)	38 (34.9)	236 (33.6)	413 (35.4)	0.416	0.977	0.485
Lesion: % stenosis	57.6±12.4	57.3±9.7	59.2±11.4	56.7±13.1	0.013	0.850	55.4±13.9	58.7±13.3	56.9±13.2	54.2±14.3	<0.001	0.009	<0.001
Stenosis severity, n (%)													
0%–49%	118 (16.4)	3 (8.3)	34 (13.8)	81 (18.6)	0.069	0.278	505 (25.5)	17 (15.6)	151 (21.5)	337 (28.9)	0.001	0.013	0.10
50%–69%	436 (60.7)	27 (75.0)	147 (59.5)	262 (60.2)			1079 (54.6)	59 (54.1)	397 (56.5)	623 (53.4)			
70%–89%	150 (20.9)	6 (16.7)	63 (25.5)	81 (18.6)			343 (17.3)	29 (26.6)	139 (19.8)	175 (15.0)			
≥90%	14 (1.9)	0 (0.0)	3 (1.2)	11 (2.5)			51 (2.6)	4 (3.7)	16 (2.3)	31 (2.7)			
ACC/AHA class. B2/C, n (%)	310 (43.2)	17 (48.6)	115 (46.6)	178 (40.9)	0.153	0.514	757 (38.3)	51 (46.8)	311 (44.2)	395 (33.9)	<0.001	0.060	0.020
Vessel Ref. diameter, mm	2.97±0.53	2.94±0.53	2.93±0.52	3.00±0.54	0.057	0.677	2.91±0.54	2.83±0.56	2.88±0.54	2.94±0.54	0.023	0.113	0.005
Lesion: length, mm	13.7±7.2	14.5±8.9	14.3±8.0	13.3±6.6	0.062	0.570	13.6±7.9	16.9±12.6	13.9±7.9	13.2±7.3	0.033	<0.001	0.916
FFR results													
FFR (all lesions)	0.82±0.09	0.81±0.05	0.78±0.10	0.84±0.10	<0.001	0.655	0.82±0.10	0.78±0.12	0.79±0.12	0.84±0.10	<0.001	<0.001	0.764
Lesions with FFR≤0.80, n (%)	288 (40.0)	18 (50.0)	145 (58.7)	125 (28.6)	<0.001	0.209	786 (39.7)	78 (71.6)	381 (54.2)	327 (28.0)	<0.001	<0.001	0.902

ACS indicates acute coronary syndrome; and FFR, fractional flow reserve.
**P* values comparing ACS vs non-ACS populations.
†*P* values comparing in ACS FFR used vs FFR disregarded populations.
‡*P* values comparing in non-ACS FFR used vs FFR disregarded populations.
§*P* values comparing in FFR used, ACS reclassified vs ACS nonreclassified populations.
‖*P* values comparing in FFR used, non-ACS reclassified vs non-ACS nonreclassified populations.

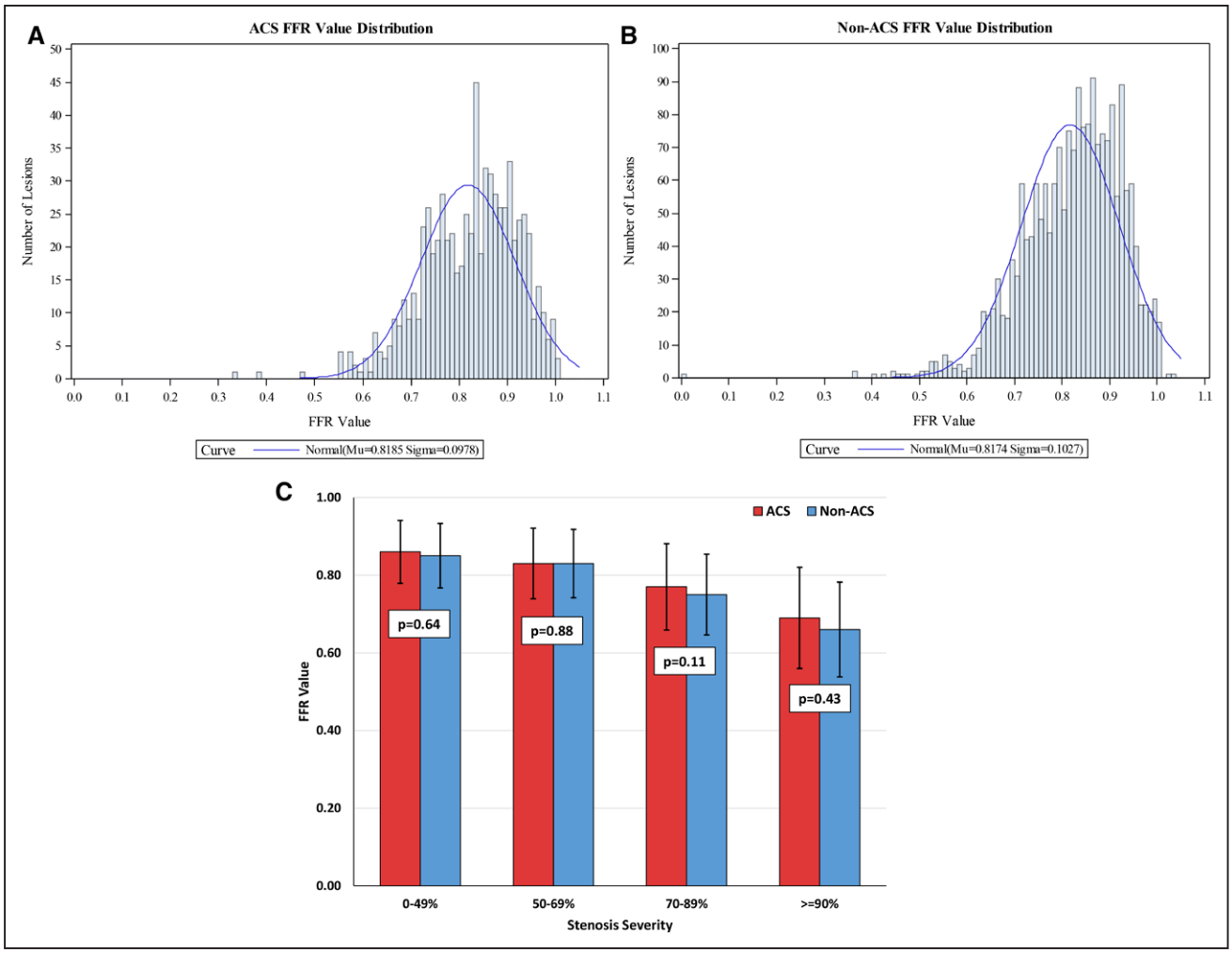

Figure 2. A, Fractional flow reserve (FFR) value distribution in the acute coronary syndrome (ACS) population. **B**, FFR value distribution in the non-ACS population. **C**, FFR value stratified by the stenosis severity group. A similar normal distribution of FFR values was observed in patients with both ACS and non-ACS. No difference in FFR value was observed between patients with ACS and non-ACS in each of the stratum of stenosis severity.

FFR-Based Reclassification of Management Strategy and Clinical Outcome in Patients With ACS

Among the 499 patients with ACS in whom FFR was used for decision, reclassification of the management strategy (ie, FFR-based decision discordant with angiography; n=188) was safe. These patients had a 1-year clinical outcome at least as good as in those (n=311) in whom the decision was not reclassified by FFR (ie, FFR-based decision concordant with angiography): 1-year MACE rate of 8.0% versus 11.6%, respectively (log rank *P*=0.20; Table 3; Figures 1 and 4A). These findings were consistent irrespective of the initial revascularization strategy (Figure III in the Data Supplement) and were not modified after multivariable adjustment (Table 4, analysis by ACS and reclassification status). A similar pattern was observed for the combined rate of death/MI (4.3% versus 7.7%; log rank *P*=0.13), the rate of MI or unplanned coronary revascularization (Table 3), or the proportion of patients free from angina at 1 year (92.3 versus 94.8, *P*=0.25). As reported previously, reclassification of the management strategy was also safe in patients with non-ACS (Figures 1 and 3; Table 3).

FFR-Based Deferral of Revascularization in ACS: Patient Profile and Clinical Outcome

Among those in whom FFR was used to drive the final decision, patients with ACS were less frequently deferred to medical treatment (all lesions deferred) than patients with non-ACS (237/499 [47%] versus 721/1353 [53%]; *P*=0.01; Table 5). Deferred patients were older, but had less risk factors than those not deferred (Table III in the Data Supplement). As expected, deferred patients were also less likely to have 2- to 3-vessel CAD (<0.01), an left anterior descending lesion (<0.01), angiographically complex disease (<0.01), and severe lesions (<0.01), while having a much high FFR value (*P*<0.001; Table IV in the Data Supplement).

Importantly, in the ACS cohort, FFR-based deferral identified a group of patients at lower risk of 1-year MACE (8.0%), as compared with the remainder of the ACS population. The rate of MACE in the former was lower than in nondeferred patients with ACS (12.3%; *P*=0.09; Table 5; Figure 4B) and of the same magnitude as in patients with non-ACS deferred (8.5%; *P*=0.83; Table 5; Figure 4B). These findings were consistent after multivariable adjustment (Table 4, analysis by ACS and deferral status).

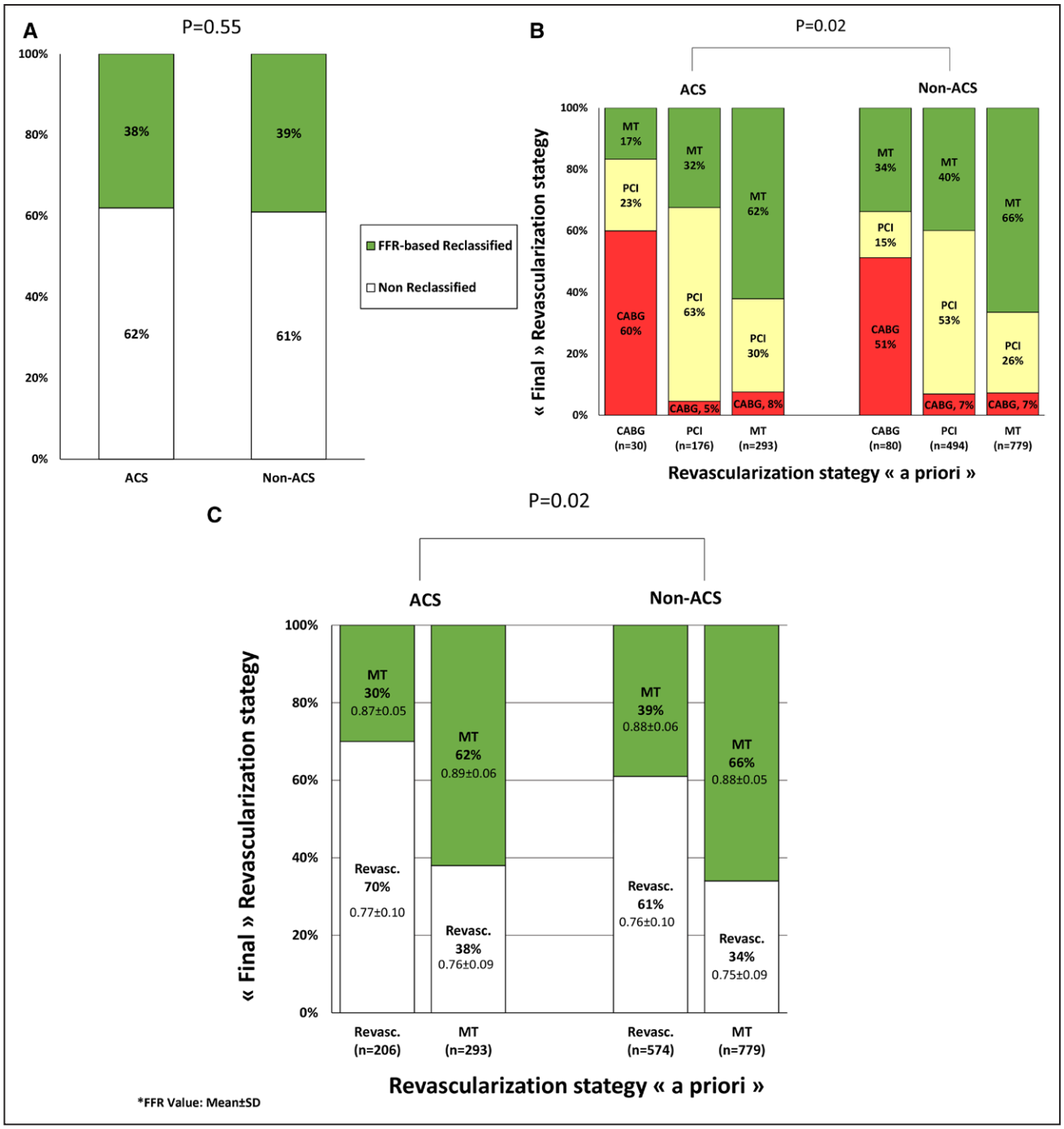

Figure 3. A, Overall rate of fractional flow reserve (FFR)–based reclassification of the revascularization strategy in patients with acute coronary syndrome (ACS) and non-ACS. **B**, Detailed description of the FFR-based reclassification of the revascularization strategy according to the revascularization strategy a priori in patients with ACS and non-ACS. For this illustration, 3 groups of revascularization strategy are considered: (1) medical treatment, (2) percutaneous coronary intervention (PCI), and (3) coronary artery bypass grafting (CABG). **C**, Identical to **B** with 2 groups of a revascularization strategy considered: (1) medical treatment and (2) revascularization (PCI/CABG). MT indicates medical treatment.

FFR Disregarded: Patient Profile and Clinical Outcome

The baseline clinical and angiographic characteristics of the 121 patients (ACS n=34 and non-ACS n=97; 6% of total population) in whom FFR data were not used for the final decision (FFR disregarded) are presented in Tables 1 and 2. Although clinical and angiographic characteristics were similar between the 2 groups (FFR disregarded versus FFR used), patients in whom FFR values were disregarded tended to have a higher proportion of lesions with FFR≤0.80 both in the ACS (50% versus 39.5%; *P*=0.2) and non-ACS (71.6% versus 37.9%; *P*<0.001) population.

In these 121 patients, the MACE rate at 1 year was twice as high as in the 1862 patients in whom the FFR information was used for final decision (23/121 [19%] versus 172/1862 [9.2%]; *P*=0.0008). Similarly, patients in whom FFR was

Table 3. Clinical Outcomes at 12 Months According to Clinical Presentation (ACS and Non-ACS) and FFR-Driven Reclassification Status

Analysis Group	MACE	Death/MI	Total Death	Myocardial Infarction	Unplanned Coronary Revascularization
ACS FFR used (n=499)	51 (10.2%)	32 (6.4%)	23 (4.6%)	13 (2.6%)	26 (5.2%)
ACS maintained (n=311, 62%)	36 (11.6%)	24 (7.7%)	17 (5.5%)	11 (3.5%)	19 (6.1%)
ACS reclassified (n=188, 38%)	15 (8.0%)	8 (4.3%)	6 (3.2%)	2 (1.1%)	7 (3.7%)
P value (log rank)	0.20	0.13	0.24	0.11	0.24
Non-ACS FFR used(n=1353)	121 (9.0%)	42 (3.1%)	27 (2.0%)	16 (1.2%)	89 (6.6%)
Non-ACS maintained (n=822, 61%)	72 (8.8%)	28 (3.4%)	17 (2.1%)	11 (1.3%)	52 (6.4%)
Non-ACS reclassified (n=531, 39%)	49 (9.2%)	14 (2.6%)	10 (1.9%)	5 (0.9%)	37 (7.0%)
P value (log rank)	0.77	0.42	0.82	0.51	0.64

Data represented as count (%); percentages based on patients with available data. ACS indicates acute coronary syndrome; FFR, fractional flow reserve; MACE, major cardiovascular event; and MI, myocardial infarction.

disregarded tended to have more angina at 1 year than those in whom FFR was used for the final decision (12% versus 7%; *P*=0.1). These findings were consistent across both ACS and non-ACS groups (Figure 1; Figure IV in the Data Supplement; Table 4, analysis by ACS and FFR usage).

FFR-Based Reclassification/Deferral and Clinical Outcome in Ongoing NSTEMI/UA and in Patients Investigated at the Culprit Vessel

Among patients with ACS (n=533), clinical outcome subanalyses were performed in 2 subgroups of interest that were identified according to study definitions: patients with an ongoing-NSTEMI/UA and those with single-vessel-CAD. The former is an important subgroup because it represents the most acute patients among our study population, whereas the latter is an even more important one because it is the only clinical situation in which the culprit nature of the investigated vessel can be ascertained.

The results in each of the 2 subpopulations—ongoing-NSTEMI/UA and single-vessel CAD ACS (illustrative of patients investigated at the culprit vessel)—were consistent with the analysis performed in the whole ACS cohort. No heterogeneity was found in the trends of MACE, associated with either overall management reclassification or, specifically, revascularization deferral (*P*>0.5 for all interaction tests; Tables V and VI in the Data Supplement). Similar to the findings in the overall population, the analysis restricted to patients with single-vessel CAD demonstrated that FFR-driven reclassification

Table 4. Results of Cox Model Analysis by ACS and Reclassification Status, by ACS and Deferral Status and by ACS and FFR Usage

	Unadjusted*		Multivariable Complete Case Only†		Multiple Imputation‡	
Comparison	HR (CI)	*P* Value	HR (CI)	*P* Value	HR (CI)	*P* Value
Analysis by ACS and reclassification status						
ACS (reclassified vs nonreclassified)	0.67 (0.37–1.23)	0.201	0.63 (0.34–1.16)	0.140	0.63 (0.34–1.16)	0.136
Non-ACS (reclassified vs nonreclassified)	1.06 (0.73–1.52)	0.772	0.99 (0.68–1.46)	0.971	1.04 (0.72–1.51)	0.833
Analysis by ACS and deferral status						
ACS (all lesion deferred vs at least 1 revascularization)	0.65 (0.37–1.14)	0.131	0.65 (0.35–1.23)	0.187	0.63 (0.34–1.19)	0.159
Non-ACS (all lesion deferred vs at least 1 revascularization)	0.89 (0.62–1.27)	0.514	0.97 (0.61–1.56)	0.907	0.88 (0.56–1.40)	0.596
All lesions deferred (ACS vs non-ACS)	0.95 (0.57–1.58)	0.834	1.01 (0.60–1.69)	0.980	0.97 (0.58–1.62)	0.893
Analysis by ACS and FFR usage						
ACS (FFR disregarded vs FFR used)	2.10 (0.95–4.63)	0.065	2.00 (0.91–4.42)	0.087	2.01 (0.91–4.45)	0.084
Non-ACS (FFR disregarded vs FFR used)	1.92 (1.14–3.23)	0.014	1.91 (1.13–3.23)	0.015	1.83 (1.09–3.09)	0.023

ACS indicates acute coronary syndrome; CI, confidence interval; FFR, fractional flow reserve; and HR, hazard ratio.

*Cox proportional hazards model without adjusting for baseline characteristics.

†Cox proportional hazards model controlling for baseline characteristics including for analysis by ACS and reclassification status: age, sex, history of diabetes mellitus, history of hypertension, high cholesterol, number of diseased vessels, FFR value, initial decision and final decision; and for analysis by ACS and deferral status: the same covariates than for analysis by ACS and reclassification status minus the final decision that was omitted. These analyses are using only using subjects with complete case of baseline covariate data.

‡Cox proportional hazards model controlling for baseline characteristics using multiple imputation method to impute missing baseline covariate data.

was as safe in ACS (hazard ratio [HR] for MACE=0.63 [0.24–1.71]; *P*=0.37) as in non-ACS (HR=0.94 [0.55–1.81]; *P*=0.82; Figure 5A), whereas FFR-based deferral of patients with ACS was associated with a similarly good outcome as in patients with non-ACS (HR for MACE in deferred non-ACS versus deferred ACS=0.91 [0.47–1.74]; *P*=0.77; Figure 5B).

Discussion

To our best knowledge, this is the largest prospective study ever to report on the use of FFR in patients with ACS undergoing angiography and its impact on treatment decisions and on clinical outcomes. In the merged PRIME-FFR cohort, from the 1983 patients enrolled in 40 centers in 2 European countries (R3F and POST-IT studies),[6,17] 533 were identified as sustaining an ongoing or recent ACS (Figure 1). The key findings of our study are (1) that the overall reclassification rate of patient management strategy is high in patients with ACS (38%) and similar to the one observed in non-ACS although the pattern of reclassification was different (Figure 3), (2) that integrating FFR information to reclassify patient management is safe in patients with ACS and that, in particular, FFR-based deferral to medical treatment is as safe in patients with ACS as it is in patients with non-ACS (Figures 4 and 5), (3) that the diagnostic value of FFR is preserved in patients in whom the culprit vessel is unambiguously investigated as reported in patients with single-vessel CAD, and (4) that disregarding the information derived from FFR is associated with a dire outcome in both groups, but more so in patients in ACS.

Change in Management Strategy in Patients With ACS

We demonstrated that patients with ACS and non-ACS had a similar overall high reclassification rate. However, the pattern of change between management strategies was different. Patients with ACS were more likely to be reclassified into one of the revascularization strategies (PCI or CABG) and less likely than patients with non-ACS to move from revascularization to medical therapy (Table 1; Figure 3B and 3C; Figure II in the Data Supplement). This finding may be the result of patients with ACS having a more complex disease profile, namely, with a higher proportion of B2/C lesions (Table 2). We reported previously that such B2/C lesions were predictive of lower FFR values, regardless of diameter stenosis severity.[6] This was further confirmed in the present data set, both in patients with ACS and in stable patients (Table II in the Data Supplement). The observation that within each category of stenosis severity, FFR was lower in more complex lesions (B2/C versus A/B1; Table I in the Data Supplement) was further supportive of this explanation. The importance of lesion complexity is frequently underestimated when assessing lesion functional severity based on angio eyeballing alone, potentially making the operators more likely to consider for a priori medical therapy, a lesion that ended up warranting revascularization after FFR was known.

The present study also extends to the ACS population the previous observation from both the R3F[6] and the POST-IT[17] studies that the routine integration of FFR on management decisions does not necessarily reduce the overall percentage of patients undergoing revascularization (namely, PCI), contrary to common belief.

Only one other study, the FAMOUS-NSTEMI trial (Fractional Flow Reserve Versus Angiography in Guiding Management to Optimize Outcomes in Non–ST-Elevation Myocardial Infarction), has evaluated the impact of FFR in management decisions of patients with ACS and found a lower reclassification rate of 21%.[7] Reasons for this discrepancy may be several. However, it is likely related to the distribution of lesions within each study. In our cohort, the proportion of truly intermediate stenosis (50%–70%) that were interrogated was higher than in FAMOUS-NSTEMI; for these lesions, treatment change is more likely to occur. Conversely, in that landmark randomized trial,[7] all lesions ≥30% (and not excluding the tightest ones) had to be interrogated per protocol, thus rendering the impact of FFR potentially less pronounced.

Integrating and Relying on FFR for Treatment Decision Is Safe in Patients With ACS

Our study clearly shows that not only is it safe to pursue a treatment strategy different from angiography but also not integrating FFR in the management workout is associated with an ominous clinical outcome. This was as true for patients

Table 5. Clinical Outcomes at 12 Months by Management Strategy: Deferred Versus Nondeferred Patients

Analysis Group	MACE	Death/MI	Total Death	Myocardial Infarction	Unplanned Coronary Revascularization
ACS FFR used (n=499)					
ACS-deferred (n=237, 47%)	19 (8.0%)	12 (5.1%)	10 (4.2%)	3 (1.3%)	9 (3.8%)
ACS-nondeferred (n=262, 53%)	32 (12.3%)	20 (7.7%)	13 (5.0%)	10 (3.8%)	17 (6.5%)
P value (log rank)	0.09	0.25	0.70	0.09	0.19
Non-ACS FFR used (n=1353)					
Non-ACS-deferred (n=721, 53%)	61 (8.5%)	24 (3.3%)	17 (2.4%)	7 (1.0%)	42 (5.9%)
Non-ACS-nondeferred (n=632, 47%) 47%)	60 (9.5%)	18 (2.9%)	10 (1.6%)	9 (1.4%)	47 (7.4%)
P value (log rank)	0.51	0.60	0.31	0.45	0.24
P value (ACS-deferred vs non-ACS deferred, log rank)	0.83	0.23	0.14	0.70	0.24

Data represented as count (%). ACS indicates acute coronary syndrome; deferred patients, all lesions deferred by FFR; FFR, fractional flow reserve; MACE, major cardiovascular event; MI, myocardial infarction; and Nondeferred patients, at least 1 lesion revascularized (percutaneous coronary intervention or coronary artery bypass grafting).

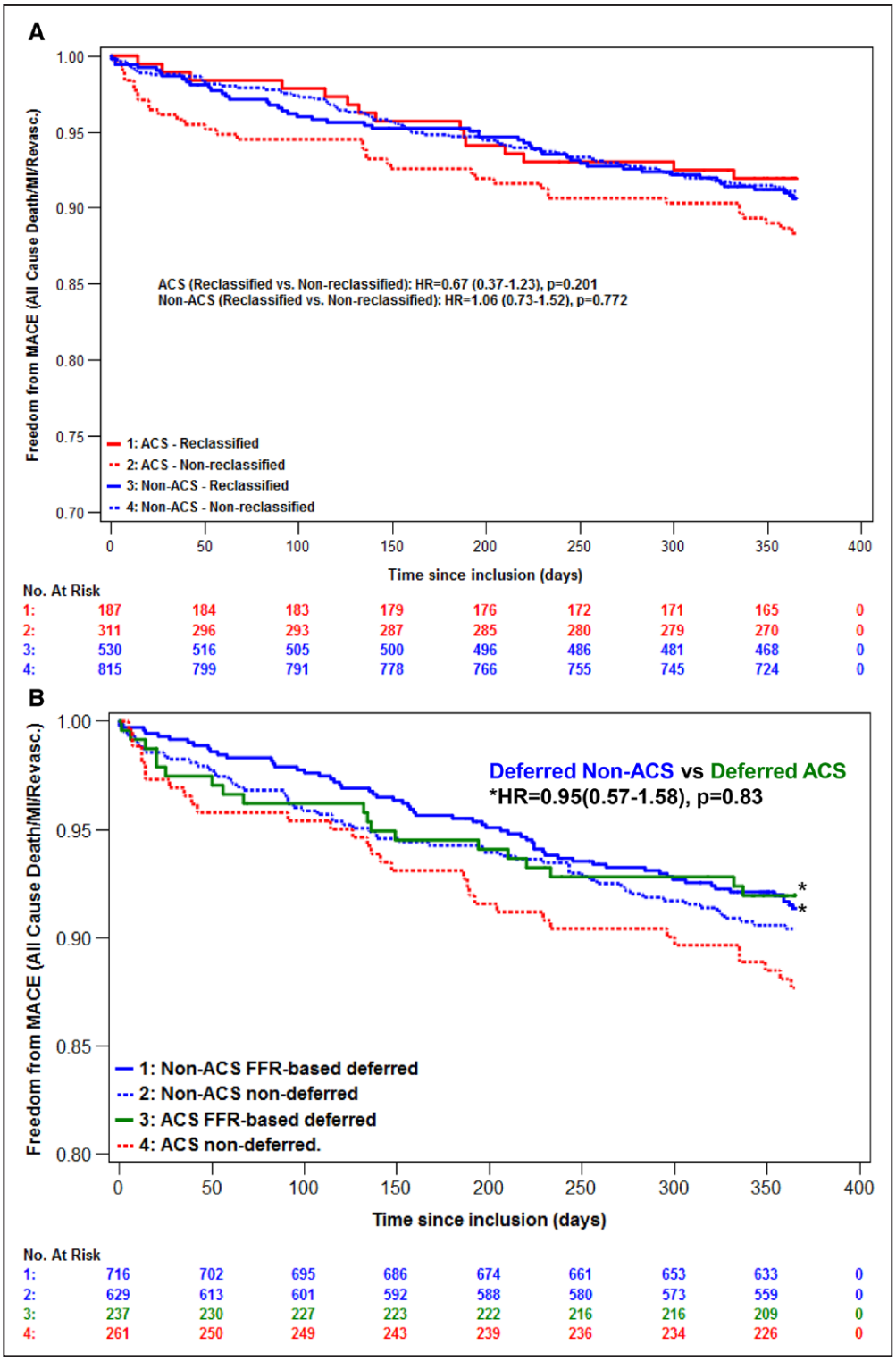

Figure 4. Fractional flow reserve (FFR)–based decision and clinical outcome in the overall acute coronary syndrome (ACS) population. **A**, FFR-based reclassification of the patient coronary revascularization strategy in patients with ACS: impact on 1-y outcome. Patients with non-ACS are presented for comparison. FFR-based reclassification (FFR against angiography) was safe in patients with ACS (plain red line). **B**, Safety of FFR-based deferral to medical treatment in patients with ACS: impact on 1-y outcome. Patients with non-ACS are presented for comparison. FFR-based deferral to medical treatment was as safe in ACS (green line) as it was in non-ACS (blue line). HR indicates hazard ratio; and MACE, major cardiovascular event.

with ACS as for patients with non-ACS , and actually the magnitude of the difference in the outcomes was even more pronounced in the ACS group. Indeed, despite patients with ACS having a higher coronary disease burden and complexity (Table 2), the rate of all end points was similar in reclassified, relative to nonreclassified patients (Table 3), meaning that

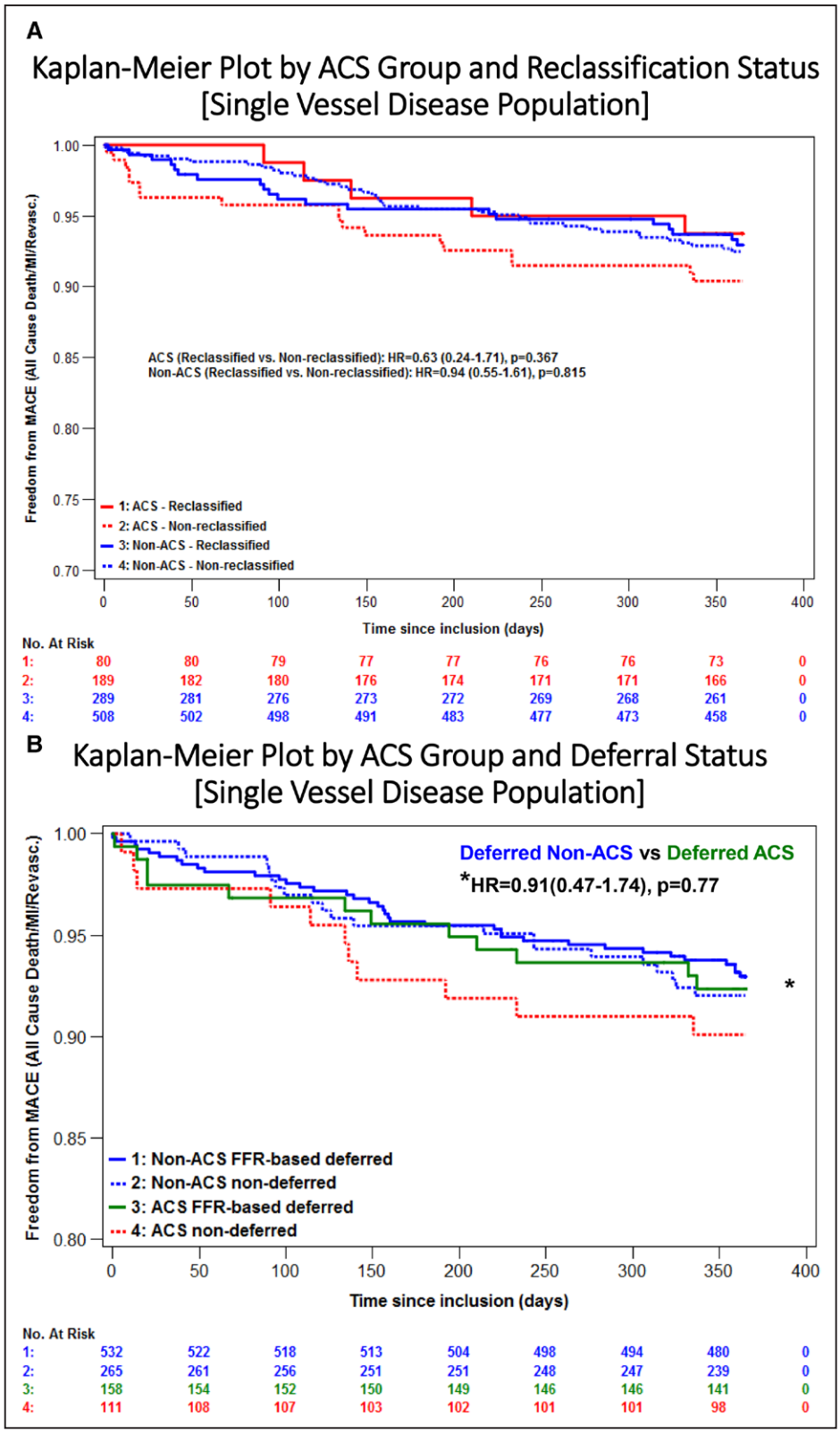

Figure 5. Fractional flow reserve (FFR)–based decision and clinical outcome in patients with acute coronary syndrome (ACS) investigated at the culprit vessel (ACS patients with single-vessel coronary artery disease [CAD]). **A**, FFR-based reclassification of the patient coronary revascularization strategy in ACS patients with single-vessel CAD: impact on 1-y outcome. Patients with non-ACS are presented for comparison. FFR-based reclassification (FFR against angiography) was safe in patients with ACS (plain red line). **B**, Safety of FFR-based deferral to medical treatment in ACS patients with single-vessel CAD: impact on 1-y outcome. Patients with non-ACS are presented for comparison. FFR-based deferral to medical treatment was as safe in ACS (green line) as it was in non-ACS (blue line).

neither prognosis nor symptom status of patients with ACS were jeopardized when treated against angiography. This is an important addition to the results of the FAMOUS-NSTEMI randomized trial, which was not powered to assess for differences in clinical outcomes, and in which the specific clinical outcome of patients reclassified by FFR was not reported.[7]

Although there were no protocol-mandated recommendations as to what vessels should be evaluated and how to use the information derived from FFR, the majority of patients were treated according to the FFR result. In ≈6% of cases in both the ACS and non-ACS groups, FFR was disregarded for treatment decision. It is noteworthy that these patients were nearly twice as likely to experience adverse events during the 12-month follow-up, both in the ACS and in the non-ACS cohorts (Table 4; Figure II in the Data Supplement). However, despite adequate statistical corrections for relevant baseline differences, it is still difficult to definitively exclude bias (related to unmeasured comorbidity such as patient frailty and lesion complexity) and claim causality. Nevertheless, a plausible explanation for the worse outcome may rely on the fact that the majority of patients (67.9%) in whom FFR was disregarded for treatment decision had lesions with an FFR<0.80 that were left untreated and that 60% of the reported events were actually unplanned revascularizations. This is line with the observations from both the FAME II trial (The Fractional Flow Reserve–Guided PCI Versus Medical Therapy in Stable Coronary Disease Study) and the POST-IT study.[2,17] Furthermore, it reinforces the importance of fully integrating FFR findings into treatment decisions, to minimize the risk of adverse clinical events.

Deferring Lesions Based on FFR in Patients With ACS Entails a Good Clinical Outcome

Demonstration of the safety of deferring a patient with ACS to medical treatment is another key finding of the present study. It is relevant that the incidence of the study composite primary end point at 12 months was similar in those patients with ACS and non-ACS in whom all lesions were deferred based on an FFR>0.80, and no revascularization was undertaken (Figure 5; Table 5). No dedicated randomized trial or subgroup analysis has specifically addressed the fate of lesions deferred in the context of ACS. A single-center retrospective study including 334 patients with ACS over an 8-year period, observed an 8% increase in the risk of the composite end point of cardiovascular death, MI, or differed lesion failure at 4.5±2.1 years, per every 0.01 decrease in FFR, in deferred lesions with FFR>0.80. Importantly, in that study, the primary end point was mainly driven by ad hoc revascularization and not by MI or cardiovascular death related to the deferred lesions.[21] In a subanalysis of the FAME-I study, the authors compared FFR-guided versus angio-guided revascularization in 328 ACS versus all stable angina patients; they concluded that the risk difference favoring the FFR-guided approach was similar in both groups. However, despite the number of deferred lesions might have been intuitively higher in the FFR-guided group, there was no report on their specific outcome.[15] Finally, in the recent DANAMI-3 PRIMULTI trial (the Third Danish Study of Optimal Acute Treatment of Patients With ST-Segment Elevation Myocardial Infarction; Primary PCI in Multivessel Disease), STEMI patients randomly allocated to FFR-guided revascularization of nonculprit lesions had a better clinical outcome when compared with those with no further invasive treatment. The authors reported that in the 97 patients whose revascularization was deferred based on an FFR>0.80, the outcome did not differ from the remainder of the group, suggesting that deferral is safe in this setting.[14] Finally, in the recent COMPARE-ACUTE trial (Randomised Trial of FFR-Guided Complete Revascularization Versus Infarct Artery Only Treatment in Multivessel STEMI Patients), 1-year MACCE rate was the lowest in the subgroup of 134 STEMI patients whose nonculprit lesions (evaluated acutely during primary PCI) had a known FFR>0.80.[22] Overall, our results reinforce the potential role of FFR in this setting and demonstrate that in patients diagnosed with an ACS, in whom operators feel that FFR is appropriate for decision making, an FFR value of >0.80 in all investigated lesions reliably identifies a group of patients at a lower risk of events (when compared to those were PCI or CABG is deemed necessary by FFR) and indicates that revascularization can be safely deferred (Figure 5; Table 5).

Role of Time and Reliability of FFR at Culprit Vessel in Patients With ACS

Two important findings of the present study are the demonstration of the safety of FFR-based reclassification and FFR-based deferral in patients with ongoing NSTEM/UA and in patients in whom FFR was performed at the culprit vessel. In the context of NSTEMI/UA, there is no definitive way to fully determine whether FFR is being performed at the culprit vessel or not, at the noticeable exception of patients with ACS with single-vessel disease.[13] This is why, as performed by Layland et al,[13] it was key to specifically investigate the subgroup of patients with single-vessel disease ACS and to demonstrate that the safety of the FFR-based management was preserved in these patients.

Our findings are important because the reliability of FFR to guide management decisions in patients with ACS has been challenged by the potential for microcirculatory hyporesponsiveness that has been observed within the first days of the acute event. In addition, patients with ACS frequently have >1 lesion suitable for revascularization and the identification of the culprit lesion is not always straightforward, particularly when stenosis are intermediate at angiography. Also, the coexistence of multiple lesions with features of instability is a common finding in patients with ACS.[23] Thus, the issue of whether FFR values (and subsequent decisions) are reliable, irrespective of the timing of investigation and of whether the culprit lesion is known for certain, are of major clinical importance. Available clinical evidence on these issues is both relatively scarce and conflicting. Niccoli et al[24] measured coronary flow and pressure in nonculprit lesions of 15 patients with NSTEMI and compared it with 15 patients with stable angina. They concluded that, relative to their stable counterparts, patients with ACS were more likely to have both higher baseline and lower reductions in hyperemic myocardial resistance, leading to a higher FFR, in discordance to hyperemic stenosis resistance for any given lesion. In the study by Ntalianis et al,[12] similarly investigating the reliability of FFR measurement in nonculprit lesions in a larger cohort of 101 patients with ACS,

there was no difference on average FFR measured acutely, as compared with that evaluated at 35±4 days (0.77±0.13 versus 0.77±0.13), and in only 2 patients, the FFR value was higher than 0.8 during the acute phase and lower than 0.75 at follow-up. However, despite the authors did not specifically report on the actual proportion of cases, some variation occurred around the 0.80 cutoff (in both directions). Layland et al[13] investigated resistive reserve and microcirculatory resistance of the culprit vessels in 50 patients with NSTEMI. In that study, the culprit status of the vessel was elegantly ascertained by including only patients with single-vessel CAD. They could demonstrate that, in NSTEMI patients, the vasodilatory capacity of the microcirculation of the culprit vessel was preserved and similar to stable angina patients. Another study investigated microcirculatory resistance (using CRF and index of microcirculatory resistance) and pressure gradients (resting Pd/Pa and FFR) in the culprit vessel of STEMI patients undergoing primary PCI and then subsequently at 24 hours and 6 months. FFR at the culprit vessel was lower overtime, but only in those with microvascular obstruction on cardiac magnetic resonance at baseline.[25] Overall, these results suggest that in patients with non–ST-segment–elevation ACS, microvascular dysfunction may be less marked, and the ability to achieve hyperemia likely is sufficient to maintain the diagnostic use of FFR, both in culprit and in nonculprit vessels. Importantly, the results of our study build on those previous observations by providing information on clinical outcome and by demonstrating the safety of FFR-based management in patients with ACS, including those with ongoing NSTEMI/UA and those in whom the culprit vessel was explored by FFR.

Study Limitations

The present study is the combination of 2 nationwide prospective FFR studies, and we cannot exclude that unmeasured differences between the 2 cohorts might have influenced our findings. However, the previous published results of R3F[6] and POST-IT[17] as well as the outcome analyses performed separately in each data set demonstrated consistency between the 2 cohorts.

As the current study included patients with ACS mostly with intermediate coronary lesion(s), in whom the extensiveness of FFR investigation was left to physician's choice, we cannot exclude that this represents a lower risk subset of ACS. However, several evidences are reassuring in this respect. First, in the PRIME-FFR cohort (regardless of FFR findings and FFR-based decision), event rates (especially death/MI) in the ACS subgroup were higher than in patients with non-ACS, reflecting indeed a higher risk. Second, death/MI rates of the PRIME-FFR ACS population are within the range of previous reports, such as the FAMOUS-NSTEMI[7] study and the ACS subset of the FAME-I trial.[15] Furthermore, the baseline clinical profile of our patients with ACS was clearly worse than in the FAMOUS-NSTEMI population and comparable to the ACS subset of the FAME-I trial.[7,15]

In addition, as the present study did not include any patients with an acute STEMI, it should be acknowledged that our findings do not apply to this population.

Given its observational nature, we cannot rule out uncontrolled confounding by additional factors. However, despite its nonrandomized nature, the relevance of our findings should not be downplayed. In the setting of randomized trials, the combination of protocol-mandated procedures and highly selective inclusion and exclusion criteria frequently narrows their applicability to daily real-word practice.[26,27] In the particular case of the present prospective study, we were able to expand to a specific population with ACS the findings from previous nonrandomized prospective studies, such as the RIPCORD study (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain), the R3F, and the POST-IT studies, namely, the potential of routine use of FFR for management reclassification and the safety of lesion deferral. These findings were further supported by extensive multivariable analyses.

Finally, the present study included mostly patients with truly intermediate lesions in whom the likelihood of reclassification by FFR is expected to be at its highest. Therefore, our results may not extend to patients with angiographically severe multivessel disease and tight lesions, as those investigated in the recently reported randomized FUTURE study (Fractional Flow Reserve for Guiding Treatment Strategy in Multivessel Disease Patients),[28] which also included a significant portion of patients with ACS (46%). In FUTURE, although >90% of patients were considered for revascularization as based on angiography alone (as compared with 41% in the present PRIME-FFR), the reclassification rate was only 8% (as compared with the 38% observed in PRIME-FFR). As mentioned earlier, this could be related to a higher lesion severity (mean FFR of 0.77 as compared with 0.82 in PRIME-FFR) and explain why a clinical benefit of reclassification was not observed in the FUTURE study.[28] We must, however, be extremely cautious in interpreting the initial report of the FUTURE study as the clinical follow-up is not complete (85% of the total population reported only) and as the article is not available.

Conclusions

In patients with ACS undergoing a coronary angiography, routine use of FFR is associated with a high rate of reclassification (38%) of clinical management. A strategy guided by FFR, divergent from that suggested by angiography, including revascularization deferral, seems to be safe in these patients. Furthermore, this study extends to the ACS population, the previous observation made in the general populations of R3F, RIPCORD, and POST-IT,[5,6,17] that the ultimate effect of routine FFR at time of angiography is not to decrease the number of patients referred to revascularization, but rather to deliver the appropriate treatment to each individual patient.[26,27] However, large randomized trials, powered for clinical outcomes, are needed to further refine the role of FFR and of new physiological indexes, independent of inducible hyperemia, on patient management in this setting. Both the DEFINE-FLAIR[29] (Use of the Instantaneous Wave-Free Ratio or Fractional Flow Reserve in PCI) and iFR-SWEDEHEART[30] (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome) randomized studies—which compared FFR- with iFR-guided treatment of obstructive CAD—have included ≈20% and 38% of patients with ACS, respectively. Although no specific subgroup analysis is yet available, it will likely provide additional clarification on the subject.

Acknowledgments

We thank Isabelle Tournemire, Liliana Vitorino and Mona Tiren for her expert technical assistance and logistic support.

Sources of Funding

R3F was supported by grants from St. Jude Medical and Biotronik. POST-IT was supported by grants from St. Jude Medical. The sponsors were responsible for data collection and data monitoring. Data analysis was performed under the instruction of the authors (Drs Van Belle, Dupouy, Baptista, and Raposo).

Disclosures

Drs Van Belle, Baptista, Raposo, and Oliveira are consultants for St. Jude Medical and received Speaker's fees from Volcano. Dr Rioufol is consultant for St. Jude Medical and Boston Scientific. He received Speaker's fees from Volcano and received grants from Boston Scientific and Medtronic. The other authors report no conflicts.

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Circulation
Cardiovascular Interventions

Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients With Acute Coronary Syndromes: PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries - Implementation of FFR [Fractional Flow Reserve] in Routine Practice)

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for the PRIME-FFR Study Group

Circ Cardiovasc Interv. 2017;10:
doi: 10.1161/CIRCINTERVENTIONS.116.004296
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7640. Online ISSN: 1941-7632

Supplemental Material

Impact of routine Fractional Flow Reserve on management decision and 1-year clinical outcome of ACS patients: Insights from the POST-IT and R3F Integrated Multicenter registriEs - Implementation of FFR in Routine Practice (PRIME-FFR)

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Contents (Links)

Supplemental Methods

Patient definition and recording of baseline characteristics

Hypertension was defined as a known blood pressure >140/90 mmHg or use of antihypertensive drugs. Smoking was defined as acknowledged ceased/unceased smoking. Diabetes mellitus was defined as a fasting glucose ≥126mg/dL, use of hypoglycaemic agents, or a history of physician-diagnosed diabetes mellitus. Family history of premature CAD was defined as CAD in a male first-degree relative <55 years old or CAD in a female first-degree relative <65 years old.

Monitoring

In each study an independent Clinical Research Associate was hired for data monitoring purposes. In each centre, a minimal number of cases (n=20 in POST-ITt and n=25 in R3F) and a minimal percent of all cases (20% in Post-It and 25% in R3F) were reviewed. In centers including a small number of patients (centers with n≤20 in Post-it; n≤25 in R3F) and every time it was considered appropriate following the initial sampling review, a review of all cases of the center was performed. Monitoring included protocol compliance, as well as quality and accuracy of eCRF completion. Informed consent was checked in all patients.

Statistical Analysis

The Cox Proportional Hazards analyses were performed using three different methods. The first model evaluates event rates without adjusting for relevant baseline covariates. The second model uses an adjustment for baseline covariates but does so on a complete case basis. The third analysis adjusts for baseline covariates and utilizes multiple imputation to impute missing covariate data.

Baseline covariates were selected based on statistical significance ($p<0.10$) of demographics, clinical risk factors, and prior clinical history when comparing ACS patients to Non-ACS patients in the FFR Used Population. These variables included age, diabetes, hypertension, high cholesterol, previous myocardial infarction, previous CABG, and number of diseased vessels >50%. Previous MI and previous CABG both had a high degree of missing data (>20%) which may have contributed to statistical significance and were determined to not be missing at random. The final set of covariates entering the model were age, gender, diabetes, hypertension, high cholesterol, and number of diseased vessels >50%. Gender was added to the covariate list due to its clinical importance and use in the analyses performed in R3F and POST-IT studies.

Due to missing data in some covariates, the complete case covariate adjusted model has limitations because only subjects with complete event and covariates data are included in the model. In order to evaluate all patients adjusted by baseline covariates, the missing covariate data can be imputed.[1] The total amount of covariate missing data was small and represents 1.3% of all covariate data points with a maximum of 2.9%

per variable. After examining the quantity of missing values and potential patterns in missing values, it was determined that missing values in these covariates were missing at random (MAR).

Covariate data were imputed using standard multiple imputation modeling with a discriminant function.[2] An N of ten imputed datasets was created for each Cox Proportional Hazards analysis. The Cox model was then applied to each of the ten datasets, creating ten separate results per analysis. The final results were generated by pooling the estimates of the individual proportional hazards, accounting for the standard error within and between the models.

Supplemental Table 1. FFR value by range of % stenosis severity, angiographic complexity and ACS status.

				FFR value			
Group	**Stenosis Severity**	**Complexity**	**N**	**Mean**	**StdDev**	**StdErr**	**p-value[1]**
ACS Population	0-49%	B2/C	36	0.841	0.099	0.016	0.327
		A/B1	82	0.862	0.074	0.008	
	50-69%	B2/C	178	0.815	0.087	0.007	<.001
		A/B1	257	0.841	0.087	0.005	
	70-89%	B2/C	87	0.750	0.088	0.009	0.012
		A/B1	63	0.790	0.120	0.015	
	≥90%	B2/C	9	0.675	0.136	0.045	0.793
		A/B1	5	0.716	0.102	0.046	
Non-ACS Population	0-49%	B2/C	138	0.827	0.094	0.008	<.001
		A/B1	366	0.864	0.074	0.004	
	50-69%	B2/C	421	0.807	0.098	0.005	<.001
		A/B1	658	0.843	0.083	0.003	
	70-89%	B2/C	172	0.734	0.117	0.009	0.001
		A/B1	171	0.769	0.102	0.008	
	≥90%	B2/C	26	0.644	0.118	0.023	0.341
		A/B1	25	0.672	0.142	0.028	
Total Population	0-49%	B2/C	174	0.830	0.095	0.007	<.001
		A/B1	448	0.864	0.074	0.003	
	50-69%	B2/C	599	0.809	0.095	0.004	<.001
		A/B1	915	0.842	0.084	0.003	
	70-89%	B2/C	259	0.739	0.108	0.007	<.001
		A/B1	234	0.775	0.107	0.007	
	≥90%	B2/C	35	0.652	0.121	0.020	0.392
		A/B1	30	0.680	0.136	0.025	

[1] p-value testing lesion complexity B2/C vs. A/B1 with Wilcoxon Rank-Sum test

Supplemental Table 2. Angiographic and Clinical predictors of a lower FFR value in non-ACS and ACS patients

Predictors of a lower FFR	Non-ACS patients			ACS patients		
	Estimates	Standard Error	*p*-value	Estimates	Standard Error	*p*-value
ACC/AHA Classification B2/C	0.016	0.005	0.001	0.020	0.008	0.014
Age (years)	-0.001	0.000	<.001	-0.001	0.000	0.002
Any proximal lesion	-0.006	0.005	0.173	-0.003	0.008	0.710
Diabetes mellitus	0.005	0.005	0.263	0.003	0.008	0.717
LAD location	0.049	0.004	<.001	0.051	0.008	<.001
LVEF <=50%	0.012	0.006	0.045	0.005	0.010	0.599
Lesion - % stenosis	0.002	0.000	<.001	0.002	0.000	<.001
Lesion - Length (mm)	0.003	0.000	<.001	0.002	0.001	0.002
Male Gender	0.012	0.005	0.023	-0.009	0.009	0.346
Number of diseased vessels by angiography						
1 Diseased Vessel	0.016	0.006	0.013	0.023	0.012	0.050
2 Diseased Vessels	0.042	0.007	<.001	0.031	0.013	0.018
3 Diseased Vessels	0.047	0.008	<.001	0.045	0.014	0.001
Smoking	-0.004	0.005	0.361	0.006	0.008	0.453

Supplemental Table 3. Patient's baseline characteristics by "deferral" and ACS status (in patients in which FFR was used)

	ACS		Non-ACS					
	All Lesions Deferred (N=237)	Lesions Treated (N=262)	All Lesions Deferred (N=721)	Lesions Treated (N=632)	*p*-value[1]	*p*-value[2]	*p*-value[3]	*p*-value[4]
Demographics								
Age (years)	66.0±11.2	62.1±11.7	66.4±10.0	64.0±10.0	<.001	<.001	0.640	0.011
Male Gender	169 (71.3%)	204 (77.9%)	524 (72.7%)	506 (80.1%)	0.092	0.001	0.683	0.459
Cardiovascular risk factors								
Diabetes mellitus	61 (26.5%)	87 (34.0%)	235 (33.6%)	270 (43.5%)	0.074	<.001	0.046	0.009
Hypertension	168 (73.0%)	177 (69.1%)	540 (77.1%)	462 (74.4%)	0.344	0.244	0.206	0.112
Smoking †	93 (39.2%)	126 (48.1%)	271 (37.6%)	257 (40.7%)	0.113	0.428	0.880	0.073
High Cholesterol	148 (64.6%)	166 (65.4%)	513 (73.4%)	457 (73.8%)	0.867	0.857	0.011	0.012
Prior clinical history								
Myocardial infarction	84 (47.5%)	90 (41.9%)	163 (28.7%)	169 (32.9%)	0.267	0.131	<.001	0.022
PCI	85 (48.0%)	97 (45.1%)	270 (47.5%)	225 (43.9%)	0.566	0.236	0.894	0.755
CABG	4 (2.3%)	6 (2.8%)	35 (6.2%)	17 (3.3%)	0.740	0.029	0.042	0.713
LVEF <=50%	36 (15.2%)	43 (16.4%)	109 (15.1%)	122 (19.3%)	0.107	0.008	0.778	0.597
Cardiovascular medication								
Dual anti-platelet	139 (59.4%)	153 (60.2%)	354 (49.6%)	340 (54.2%)	0.851	0.089	0.009	0.104
Statine	177 (75.6%)	193 (76.0%)	542 (76.0%)	498 (79.7%)	0.930	0.108	0.907	0.226
ACEI/ARB	154 (66.4%)	145 (58.9%)	416 (58.6%)	367 (59.1%)	0.093	0.851	0.035	0.967
Beta-Blockers	137 (59.1%)	155 (62.0%)	427 (59.9%)	390 (62.9%)	0.508	0.260	0.822	0.803
Number of diseased vessels (>50%)								
0	58 (24.5%)	13 (5.0%)	228 (31.6%)	31 (4.9%)	<.001	<.001	0.080	0.985
1	100 (42.2%)	98 (37.4%)	307 (42.6%)	235 (37.2%)				
2	56 (23.6%)	88 (33.6%)	130 (18.0%)	220 (34.8%)				
3	23 (9.7%)	63 (24.0%)	56 (7.8%)	146 (23.1%)				
Number of lesions evaluated								
1	194 (81.9%)	181 (69.1%)	577 (80.0%)	426 (67.4%)	0.010	<.001	0.470	0.970
2	30 (12.7%)	60 (22.9%)	116 (16.1%)	153 (24.2%)				
≥3	13 (5.4%)	21 (8.0%)	28 (3.9%)	53 (8.4%)				

[1] p-values comparing ACS: All Lesions Deferred vs. Lesions Treated;
[2] p-values comparing Non-ACS: All Lesions Deferred vs. Lesions Treated;
[3] p-values comparing All Lesions Deferred: ACS vs. Non-ACS;
[4] p-values comparing Lesions Treated: ACS vs. Non-ACS;
*Wilcoxon Rank-sum test used for continuous variables and Chi-Square test used for categorical variables.
† Current or former smoker <1 year

Supplemental Table 4. Lesion's baseline angiographic and FFR characteristics by "deferral" and ACS status

	ACS		Non-ACS		p-value[1]	p-value[2]	p-value[3]	p-value[4]
	All Lesions Deferred (N=292)	Lesions Treated (N=370)	All Lesions Deferred (N=897)	Lesions Treated (N=909)				
Lesion location								
Left Anterior Descending	144 (49.7%)	237 (64.1%)	469 (52.3%)	575 (63.3%)	0.006	<.001	0.038	0.351
Circumflex	69 (23.8%)	62 (16.8%)	144 (16.1%)	122 (13.4%)				
Right Coronary Artery	63 (21.7%)	54 (14.6%)	221 (24.6%)	156 (17.2%)				
Left Main	13 (4.5%)	16 (4.3%)	56 (6.2%)	49 (5.4%)				
Bypass	1 (0.3%)	1 (0.3%)	7 (0.8%)	6 (0.7%)				
Proximal LAD	47 (16.2%)	65 (17.6%)	151 (16.8%)	201 (22.1%)	0.644	0.004	0.803	0.068
Any proximal lesion	101 (34.8%)	118 (31.9%)	311 (34.7%)	317 (34.9%)	0.427	0.914	0.961	0.301
Lesion - % stenosis	53.6±10.7	60.6±13.0	50.5±11.7	59.6±14.2	<.001	<.001	<.001	0.205
Stenosis Severity								
0-49%	69 (23.8%)	41 (11.1%)	306 (34.1%)	169 (18.6%)	<.001	<.001	0.002	0.010
50-69%	187 (64.5%)	210 (56.8%)	527 (58.8%)	463 (51.0%)				
70-89%	34 (11.7%)	105 (28.4%)	63 (7.0%)	237 (26.1%)				
≥90%	0 (0.0%)	14 (3.8%)	1 (0.1%)	39 (4.3%)				
ACC/AHA Classification B2/C	94 (32.4%)	187 (50.5%)	245 (27.3%)	428 (47.1%)	<.001	<.001	0.097	0.269
Vessel Reference Diameter (mm)	3.04±0.53	2.93±0.52	2.96±0.56	2.87±0.52	0.016	<.001	0.032	0.038
Lesion - Length (mm)	12.0±5.5	15.0±7.9	11.7±5.9	15.1±8.5	<.001	<.001	0.480	0.748
FFR (all lesions)	0.89±0.05	0.76±0.10	0.89±0.05	0.76±0.10	<.001	<.001	0.649	0.166
Lesions with FFR ≤ 0.80	6 (2.1%)	254 (68.6%)	5 (0.6%)	676 (74.4%)	<.001	<.001	0.020	0.035

[1] p-values comparing ACS: All Lesions Deferred vs. Lesions Treated
[2] p-values comparing Non-ACS: All Lesions Deferred vs. Lesions Treated
[3] p-values comparing All Lesions Deferred: ACS vs. Non-ACS
[4] p-values comparing Lesions Treated: ACS vs. Non-ACS
*Wilcoxon Rank-sum test used for continuous variables and Chi-Square test used for categorical variables.

Supplemental Table 5. Sub-group analysis: 1-year outcome according to reclassification status (A) and management strategy (B) in ongoing ACS vs. recent ACS.

ACS Group	Strategy Change	N (%)	*p*-value	MACE	*p*-value
A. Reclassification status					
Ongoing ACS		**213**		**19 (8.9%)**	
	Reclassified	74 (35%)		6 (8.1%)	
	Non-reclassified	139 (65%)	0.31 [1]	13 (9.4%)	0.52 [2]
Recent ACS		**285**		**32 (11.2%)**	
	Reclassified	113 (40%)		9 (8.0%)	
	Non-reclassified	172 (60%)		23 (13.4%)	
B. Management strategy					
Ongoing ACS		**213**		**19 (8.9%)**	
	All lesions deferred	98 (32%)		6 (6.1%)	
	At least 1 revascularized	115 (54%)	0.52 [3]	13 (11.3%)	0.62 [4]
Recent ACS		**285**		**32 (11.2%)**	
	All lesions deferred	139 (49%)		13 (9.4%)	
	At least 1 revascularized	146 (51%)		19 (13.0%)	

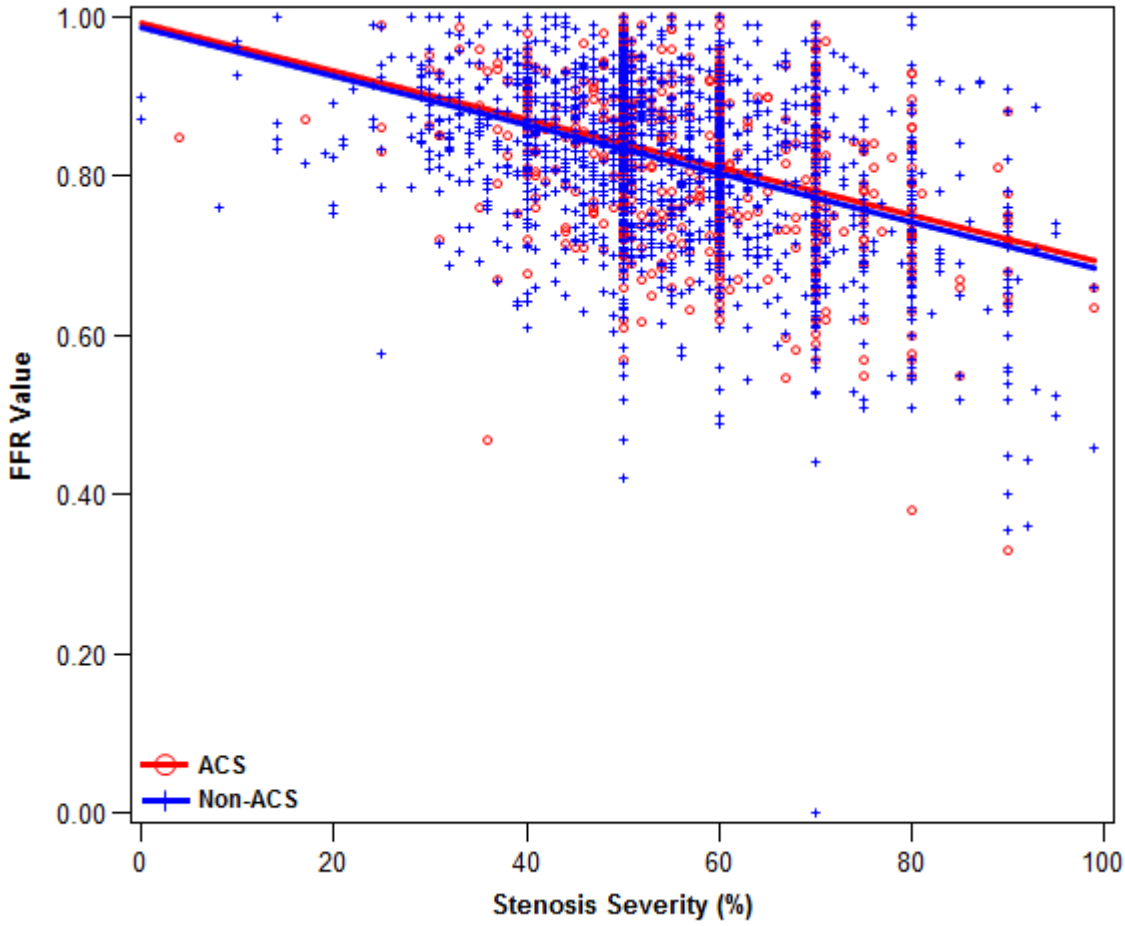
[1] p-value for the comparison of reclassification status in Ongoing ACS vs. Other ACS
[2] p-value for the interaction of ACS Type and Reclassification Status on MACE outcome
[3] p-value for the comparison of Management Strategy in Ongoing ACS vs. Other ACS
[4] p-value for the interaction of ACS Type and Management Strategy on MACE outcome

Supplemental Table 6. Sub-group analysis: 1-year outcome according to reclassification status (A) and management strategy (B) in ACS patients with "multi-vessel-CAD" (>50%) and "single-vessel-CAD"

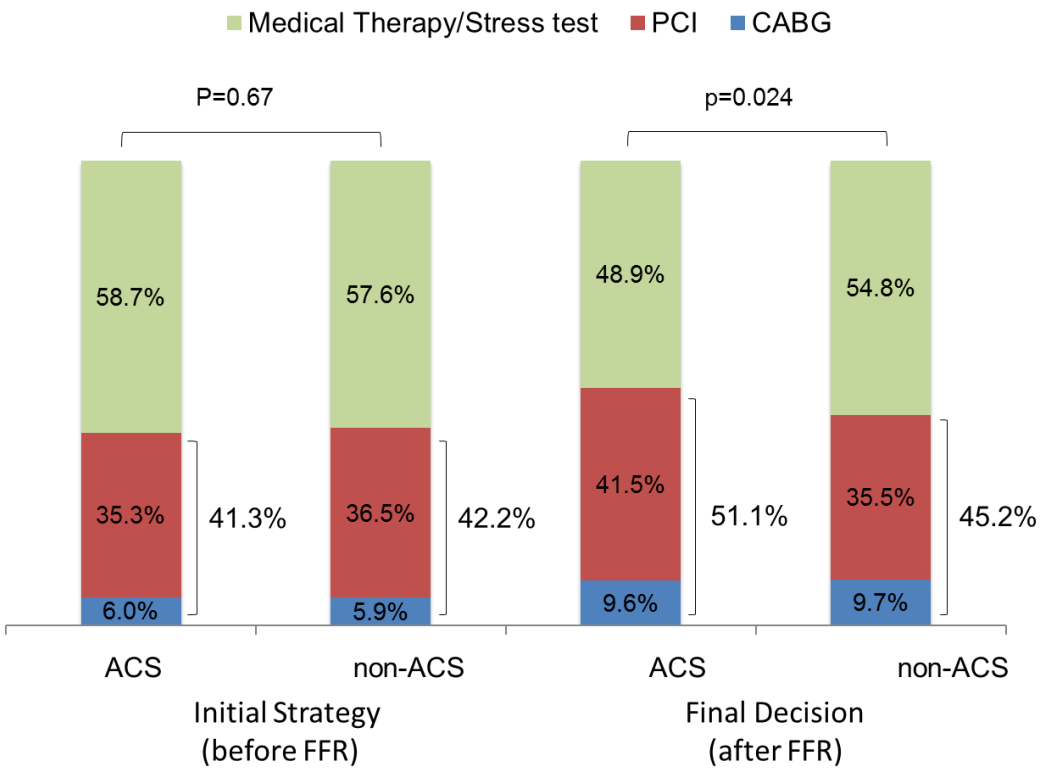
Diseased vessel group	Strategy Change	N (%)	*p*-value	MACE	*p*-value
A. Reclassification status					
Multi-vessel-CAD		**229**		**28 (12.2%)**	
	Reclassified	107 (47%)		10 (9.3%)	
	Non-reclassified	122 (53%)	<0.001 [1]	18 (14.8%)	0.97 [2]
Single-vessel-CAD		**269**		**23 (8.6%)**	
	Reclassified	80 (30%)		5 (6.3%)	
	Non-reclassified	189 (70%)		18 (9.5%)	
B. Management strategy					
Multi-vessel-CAD		**229**		**28 (12.2%)**	
	All lesions deferred	79 (34%)		7 (8.9%)	
	At least 1 revascularized	150 (66%)	<0.001 [3]	21 (14.0%)	0.76 [4]
Single-vessel-CAD		**269**		**23 (8.6%)**	
	All lesions deferred	158 (59%)		12 (7.6%)	
	At least 1 revascularized	111 (41%)		11 (9.9%)	

[1] p-value for the comparison of reclassification status in in >1 Diseased Vessels (>50%) vs. ≤1 Diseased Vessel
[2] p-value for the interaction of Vessel Disease and Reclassification Status on MACE outcome
[3] p-value for the comparison of Management Strategy in >1 Diseased Vessels (>50%) vs. ≤1 Diseased Vessel
[4] p-value for the interaction of Vessel Disease and Management Strategy on MACE outcome

Supplemental Figure 1. FFR value and stenosis severity in ACS (red) and non-ACS (blue) lesions

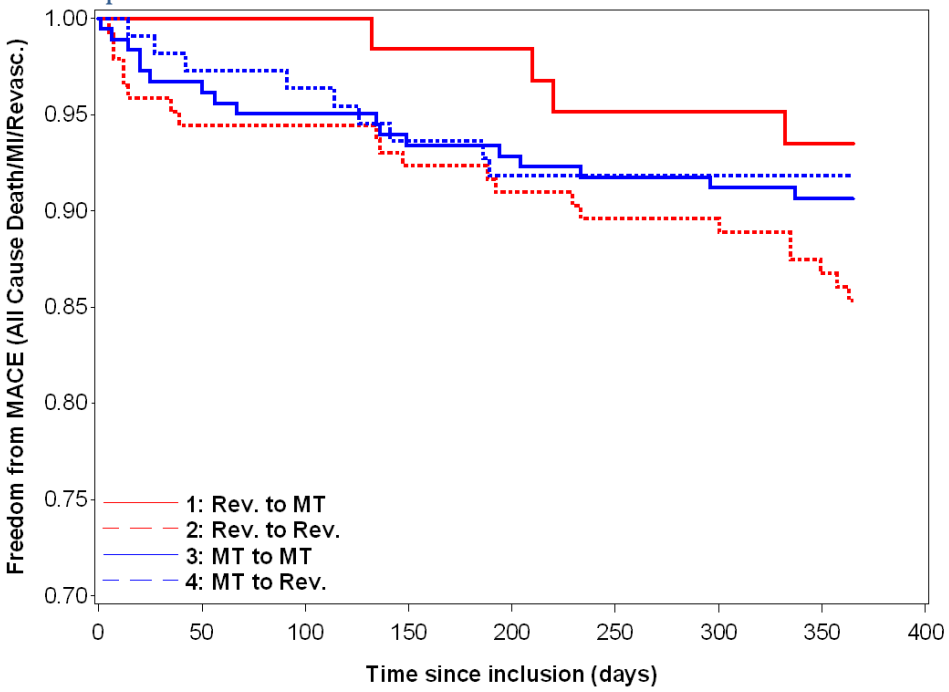


Supplemental Figure 2. Initial and Final Revascularization strategy in ACS and non-ACS patients



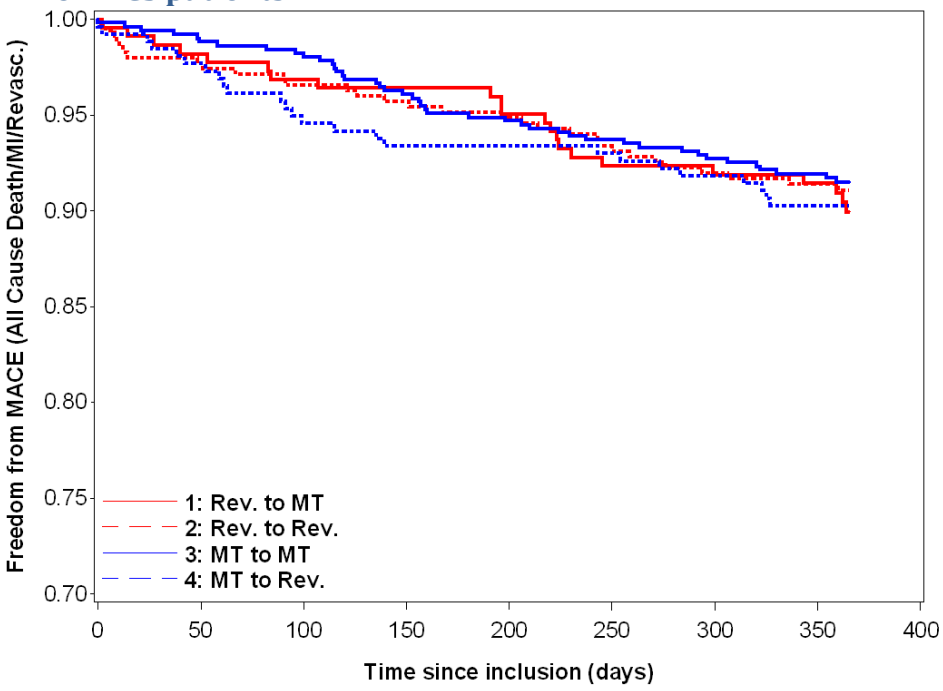
Supplemental Figure 3. One-year outcome according to reclassification status and initial revascularization strategy in ACS (A) and in non-ACS patients (B)

A – ACS patients



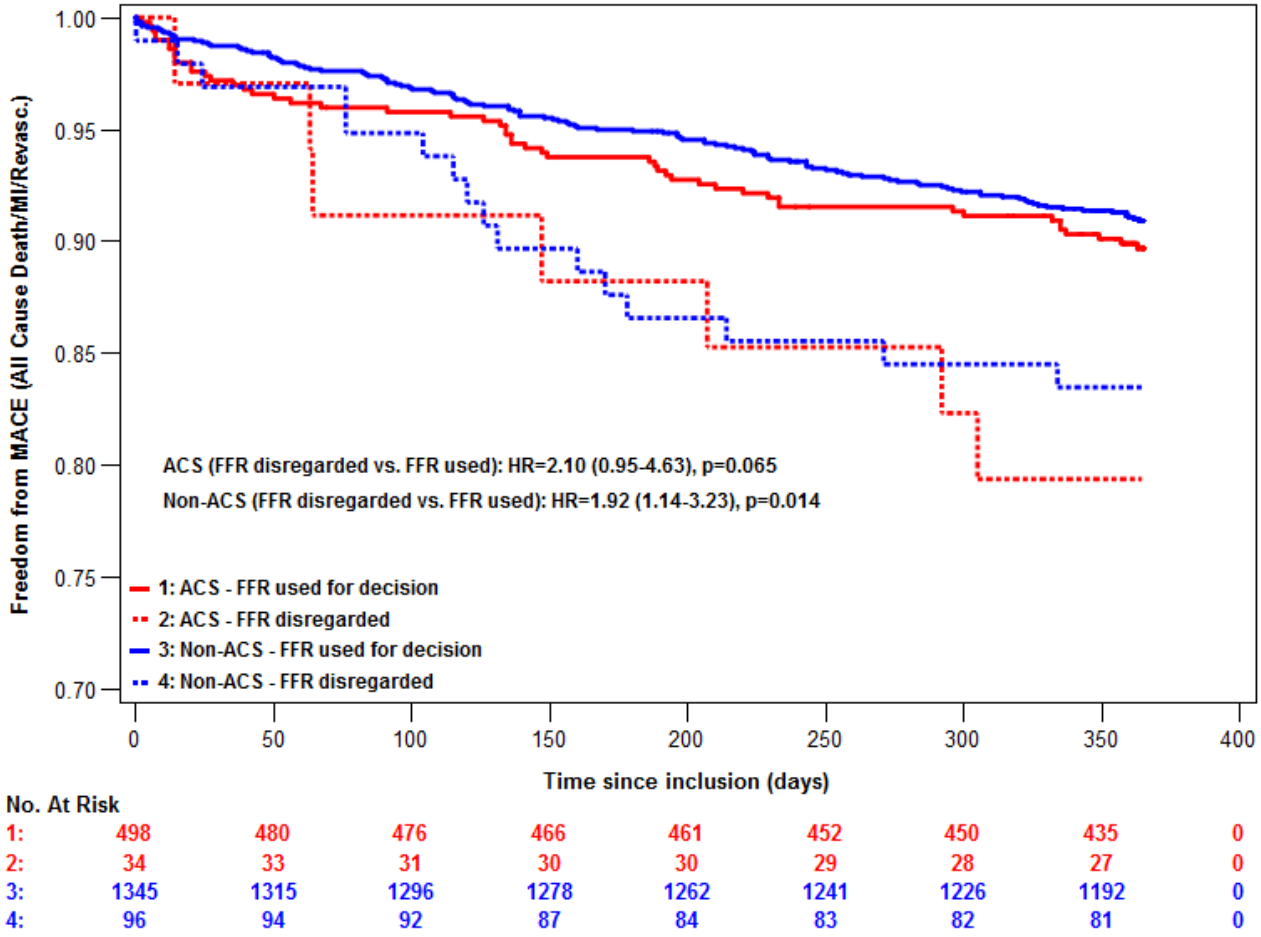
No. At Risk									
1:	62	62	62	61	61	57	57	54	0
2:	144	136	136	133	131	129	128	122	0
3:	182	175	172	169	168	165	164	160	0
4:	110	107	106	103	101	101	101	99	0

B- Non-ACS patients



No. At Risk									
1:	224	219	216	215	211	204	202	197	0
2:	348	341	337	334	331	324	320	315	0
3:	513	504	500	490	481	475	469	452	0
4:	260	251	243	239	239	238	235	228	0

Supplemental Figure 4. One-year outcome according to FFR use vs. "disregarded" in ACS and in non-ACS patients



No. At Risk									
1:	498	480	476	466	461	452	450	435	0
2:	34	33	31	30	30	29	28	27	0
3:	1345	1315	1296	1278	1262	1241	1226	1192	0
4:	96	94	92	87	84	83	82	81	0

Supplemental Figure legends

Supplemental Figure 1: Relationship between FFR value and stenosis severity (%) in ACS (red) and non-ACS (blue).

Supplemental Figure 2: Initial and Final Revascularization strategy in ACS and non-ACS patients. Before the results of the FFR was known, the initial strategy was similar between ACS- and non-ACS patients. After FFR was known (final decision), the proportion of patients submitted to PCI or CABG was higher in the ACS-group, as compared to non-ACS (p=0.02).

Supplemental Figure 3; One-year outcome according to reclassification status and initial revascularization strategy in ACS (A) and in non-ACS patients (B). For this illustration 4 groups were considered: Group 1: Revascularization (PCI or CABG) as initial strategy and medical treatment as final strategy; Group 2: Revascularization (PCI or CABG) as initial strategy and revascularization (PCI or CABG) as final strategy; Group 3: Medical treatment as initial strategy and medical treatment as final strategy; and Group 4: Medical treatment as initial strategy and revascularization (PCI or CABG) as final strategy.

Supplemental Figure 4: One-year outcome according to FFR use vs. "disregarded" in ACS and in non-ACS patients. In both ACS (red lines) and non-acs patients (blue lines), the rate of MACE at 1 year was two-fold higher in patients in patients in whom the FFR was disregarded (dashed lines) as compared to those in whom the FFR was used for clinical decision (plain lines).

Supplemental References

1. Rubin DB. Multiple Imputation after 18+ Years. *Journal of the American Statistical Association*. 1996;91: 473–489.

2. van Buuren S. Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification. *Statistical Methods in Medical Research* 2007;16:219–242.